

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/086294 A2

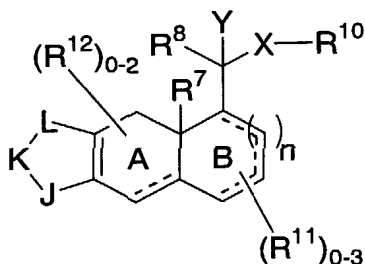
- (51) International Patent Classification⁷: **A61K**
- (21) International Application Number: PCT/US03/10867
- (22) International Filing Date: 8 April 2003 (08.04.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/371,948 11 April 2002 (11.04.2002) US
- (71) Applicant (for all designated States except US): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **ALI, Amjad** [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BALKOVEC, James, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **GRAHAM, Donald, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **THOMPSON, Christopher, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **QURAISHI, Nazia** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 1H-BENZO[F]INDAZOL-5-YL DERIVATIVES AS SELECTIVE GLUCOCORTICOID RECEPTOR MODULATORS



(I)

(57) **Abstract:** The present invention encompasses compounds of Formula I: (I) or pharmaceutically acceptable salts or hydrates thereof, which are useful as selective glucocorticoid receptor ligands for treating a variety of autoimmune and inflammatory diseases or conditions. Pharmaceutical compositions and methods of use are also included.

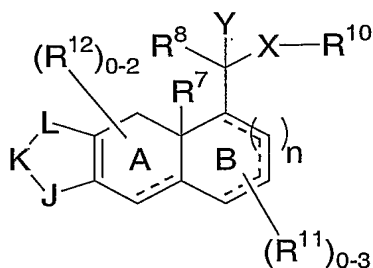
1H-BENZO[F]INDAZOL-5-YL DERIVATIVES AS SELECTIVE
GLUCOCORTICOID RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

Intracellular receptors (IR's) are a class of structurally related proteins involved in the regulation of gene expression. The steroid hormone receptors are a subset of this superfamily whose natural ligands are typically comprised of endogenous steroids such as estradiol, progesterone, and cortisol. Man-made ligands to these receptors play an important role in human health and, of these receptors, the glucocorticoid receptor has an essential role in regulating human physiology and immune response. Steroids that interact with the glucocorticoid receptor have been shown to be potent anti-inflammatory agents. The present invention is directed to a novel class of compounds that are selective glucocorticoid receptor modulators that have potent anti-inflammatory and immunosuppressive activity and possess advantages over steroidal glucocorticoid ligands with respect to side effects, efficacy, toxicity and/or metabolism.

SUMMARY OF THE INVENTION

The present invention encompasses compounds of Formula I:

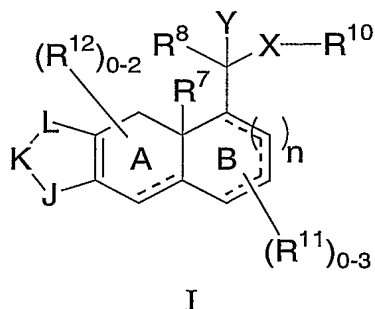


I

or pharmaceutically acceptable salts or hydrates thereof, which are useful as selective glucocorticoid receptor ligands for treating a variety of autoimmune and inflammatory diseases or conditions. Pharmaceutical compositions and methods of use are also included.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a compound represented by
Formula I



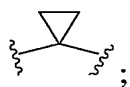
or a pharmaceutically acceptable salt or hydrate thereof, wherein:

10 n is 0, 1 or 2;

J is selected from NR^1 or $C(R^1)(R^2)$;

15 K is selected from NR^3 or $C(R^3)(R^4)$;

L is selected from NR^5 or $C(R^5)(R^6)$;

X is a bond, $-C(O)-$, $-N(R^{14})-$, $-N(R^{14})-C(O)-$, or ;

20 R^1 , R^8 and R^{10} are each independently selected from the group
consisting of:

- 25
- (1) C_{1-6} alkyl,
 - (2) C_{2-6} alkenyl,
 - (3) C_{3-6} alkynyl,
 - (4) C_{3-6} cycloalkyl,
 - (5) C_{1-6} alkoxy,
 - (6) C_{1-6} alkyl- $S(O)_k-$, wherein k is 0, 1 or 2,
 - (7) aryl,
 - (8) aralkyl,

- 5
- (9) HET,
 - (10) -C₁₋₆alkyl-HET,
 - (11) aryloxy,
 - (12) aroyloxy,
 - (13) aralkenyl,
 - (14) aralkynyl,
 - (15) hydrogen,
 - (16) hydroxy and
 - (17) C₁₋₆alkyl-N(R¹⁴)-S(O)_k-, wherein k is 0, 1 or 2,

10

wherein items (1) to (6) above and the alkyl portions of items (8), (10) and (17) above and the alkenyl portion of item (13) above and the alkynyl portion of item (14) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂, C₃₋₆cycloalkyl, C₁₋₆alkyl-S(O)_k- and aryl-S(O)_k-, wherein k is 0, 1 or 2, and

wherein items (7), (9), (11) and (12) above and aryl portion of items (8), (13) and (14) above and the HET portion of item (10) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- 20
- (a) halo,
 - (b) OR¹³,
 - (c) N(R¹⁴)₂,
 - (d) C₁₋₆alkyl,
 - (e) C₂₋₆alkenyl,
 - (f) C₃₋₆alkynyl,
 - (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
 - (h) aryl,
 - (i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
 - (j) HET,
 - (k) aralkyl,
 - (l) aroyl,
 - (m) aryloxy,
 - (n) aralkoxy and
- 25
- 30
- 35

(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and
5 N(R¹⁴)₂, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo,
10 OR¹³ and C₁₋₄alkyl,

or when X is a bond then R⁸ and R¹⁰ may be joined together to form a 4- to 8-membered monocyclic ring, optionally containing 1-3 heteroatoms selected from O, S and NR¹⁴, and optionally containing 1 or 2 double bonds;

15

R², R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of:

- (1) hydrogen,
- (2) halo,
- 20 (3) C₁₋₆alkyl,
- (4) C₂₋₆alkenyl,
- (5) C₃₋₆alkynyl,
- (6) C₃₋₆cycloalkyl,
- (7) C₁₋₆alkoxy,
- 25 (8) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (9) aryl,
- (10) aralkyl,
- (11) HET and
- (12) -C₁₋₆alkyl-HET,

30 wherein items (3) to (8) above and the alkyl portions of items (10) and (12) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂ and C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2; and

wherein items (9) and (11) and the aryl portion of items (10) and the HET portion of item (12) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- 5 (a) halo,
(b) OR¹³,
(c) N(R¹⁴)₂,
(d) C₁₋₆alkyl,
(e) C₂₋₆alkenyl,
10 (f) C₃₋₆alkynyl and
(g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,

wherein items (d) to (g) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂,

15

or R¹ and R³ or R³ and R⁵ may be joined together to form a double bond;

R⁷ is selected from the group consisting of:

- 20 (1) hydrogen,
(2) OR¹³,
(3) C₁₋₄alkyl,
(4) aryl and
(5) aralkyl,

25 wherein item (3) above and the alkyl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

30 wherein item (4) above and the aryl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
(b) OR¹³,
35 (c) N(R¹⁴)₂,

- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl and
- (f) C₃₋₆alkynyl,

wherein items (d) to (f) above are optionally substituted with from one up to the
 5 maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂;

Y is selected from the group consisting of:

- (1) hydrogen,
- 10 (2) -O-R⁹,
- (3) -S(O)_k-R⁹, wherein k is 0, 1 or 2,
- (4) -C-W-R⁹, wherein W is O or S(O)_k,
- (5) -N(R¹⁵)₂,
- (6) -S(O)_k-N(R¹⁵)₂,
- 15 (7) -N(R¹⁵)-S(O)_k-N(R¹⁵)₂,
- (8) NO₂,
- (9) -C(O)-R¹⁵,
- (10) -C(O)O-R¹⁵,
- (11) -CN,
- 20 (12) halo and
- (13) -O-S(O)_k-R¹⁵,

R⁹ is selected from the group consisting of: hydrogen, C₁₋₁₂alkyl and
 aryl, wherein C₁₋₁₂alkyl and aryl are optionally substituted from one up to the
 25 maximum number of substituents with halo, or when Y is OR⁹ then R⁸ and R⁹ may be joined together to form a carbonyl group;

each R¹¹ and R¹² is independently selected from the group consisting
 of:

- 30 (1) halo,
- (2) C₁₋₆alkyl,
- (3) C₂₋₆alkenyl,
- (4) C₁₋₆alkoxy and
- (5) hydroxy,

wherein items (2) to (4) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹², N(R¹³)₂ and C₁₋₆alkyl-S(O)_k, wherein k is 0, 1 or

5 2;

each R¹³ and R¹⁴ is independently selected from the group consisting of hydrogen, C₁₋₄alkyl and C₂₋₄alkenyl, each of said C₁₋₄alkyl and C₂₋₄alkenyl optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, C₁₋₄alkoxy, aryl, C₃₋₆cycloalkyl, CN and C₁₋₄alkyl-S(O)_k, wherein k is 0, 1 or 2;

10

each R¹⁵ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, aryl and C₁₋₁₂alkoxycarbonyl, wherein said C₁₋₆alkyl and C₁₋₁₂alkoxycarbonyl are optionally substituted from one up to the maximum number of substitutable positions with halo and said aryl is optionally substituted from one up to the maximum number of substitutable positions with halo and C₁₋₄alkyl, optionally substituted with 1-3 halo groups; and

15

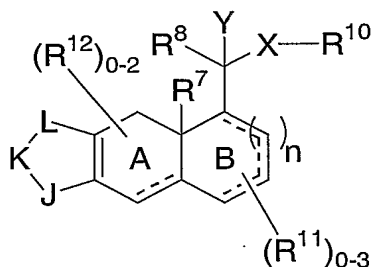
HET is a 5- to 10-membered aromatic, partially aromatic or non-aromatic mono- or bicyclic ring, containing 1-4 heteroatoms selected from O, S and N, and optionally substituted with 1-2 oxo groups.

20

An embodiment of the invention encompasses a compound of Formula

I

25



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

30

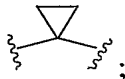
n is 0, 1 or 2;

J is selected from NR^1 or $\text{C}(\text{R}^1)(\text{R}^2)$;

5 K is selected from NR^3 or $\text{C}(\text{R}^3)(\text{R}^4)$;

L is selected from NR^5 or $\text{C}(\text{R}^5)(\text{R}^6)$;

10

X is a bond, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{14})-$, $-\text{N}(\text{R}^{14})-\text{C}(\text{O})-$, or ;

R^1 , R^8 and R^{10} are each independently selected from the group consisting of:

- (1) C_{1-6} alkyl,
- (2) C_{2-6} alkenyl,
- 15 (3) C_{3-6} alkynyl,
- (4) C_{3-6} cycloalkyl,
- (5) C_{1-6} alkoxy,
- (6) C_{1-6} alkyl- $\text{S}(\text{O})_k-$, wherein k is 0, 1 or 2,
- (7) aryl,
- 20 (8) aralkyl,
- (9) HET,
- (10) $-\text{C}_{1-6}$ alkyl-HET,
- (11) aryloxy,
- (12) aroyloxy,
- 25 (13) aralkenyl,
- (14) aralkynyl,
- (15) hydrogen,
- (16) hydroxy and

30 wherein items (1) to (6) above and the alkyl portions of items (8) and (10) above and the alkenyl portion of item (13) above and the alkynyl portion of item (14) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{13} , $\text{N}(\text{R}^{14})_2$, C_{3-6} cycloalkyl and C_{1-6} alkyl- $\text{S}(\text{O})_k-$, wherein k is 0, 1 or 2, and

wherein items (7), (9), (11) and (12) above and aryl portion of items (8), (13) and (14) above and the HET portion of item (10) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently

5 selected from the group consisting of:

- (a) halo,
- (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- 10 (e) C₂₋₆alkenyl,
- (f) C₃₋₆alkynyl,
- (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (h) aryl,
- (i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
- 15 (j) HET,
- (k) aralkyl,
- (l) aroyl,
- (m) aryloxy,
- (n) aralkoxy and
- 20 (o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

25

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and C₁₋₄alkyl,

30

or when X is a bond then R⁸ and R¹⁰ may be joined together to form a 4- to 8-membered monocyclic ring, optionally containing 1-3 heteroatoms selected from O, S and NR¹⁴, and optionally containing 1 or 2 double bonds;

R², R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of:

- (1) hydrogen,
- (2) halo,
- 5 (3) C₁₋₆alkyl,
- (4) C₂₋₆alkenyl,
- (5) C₃₋₆alkynyl,
- (6) C₃₋₆cycloalkyl,
- (7) C₁₋₆alkoxy,
- 10 (8) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (9) aryl,
- (10) aralkyl,
- (11) HET and
- (12) C₁₋₆alkyl-HET,

15 wherein items (3) to (8) above and the alkyl portions of items (10) and (12) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂ and C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2; and

20 wherein items (9) and (11) and the aryl portion of items (10) and the HET portion of item (12) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
- 25 (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl,
- (f) C₃₋₆alkynyl and
- 30 (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,

wherein items (d) to (g) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂.

or R¹ and R³ or R³ and R⁵ may be joined together to form a double bond;

R⁷ is selected from the group consisting of:

- 5 (1) hydrogen,
 (2) OR¹³,
 (3) C₁₋₄alkyl,
 (4) aryl and
 (5) aralkyl,

10 wherein item (3) above and the alkyl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

15 wherein item (4) above and the aryl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
 (b) OR¹³,
20 (c) N(R¹⁴)₂,
 (d) C₁₋₆alkyl,
 (e) C₂₋₆alkenyl and
 (f) C₃₋₆alkynyl,

 wherein items (d) to (f) above are optionally substituted with from one up to the
25 maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂;

Y is selected from the group consisting of:

- 30 (1) hydrogen,
 (2) -O-R⁹,
 (3) -S(O)_k-R⁹, wherein k is 0, 1 or 2,
 (4) -C-W-R⁹, wherein W is O or S(O)_k,
 (5) -N(R¹⁵)₂,
 (6) -S(O)_k-N(R¹⁵)₂,

- 5
- (7) -N(R¹⁵)-S(O)_k-N(R¹⁵)₂,
 - (8) NO₂,
 - (9) -C(O)-R¹⁵,
 - (10) -C(O)O-R¹⁵,
 - (11) -CN,
 - (12) halo and
 - (13) -O-S(O)_k-R¹⁵,

10 R⁹ is selected from the group consisting of: hydrogen, C₁₋₁₂alkyl and aryl, wherein C₁₋₁₂alkyl and aryl are optionally substituted from one up to the maximum number of substituents with halo, or when Y is OR⁹ then R⁸ and R⁹ may be joined together to form a carbonyl group;

15 each R¹¹ and R¹² is independently selected from the group consisting of:

- (1) halo,
- (2) C₁₋₆alkyl,
- (3) C₂₋₆alkenyl,
- (4) C₁₋₆alkoxy and
- 20 (5) hydroxy,

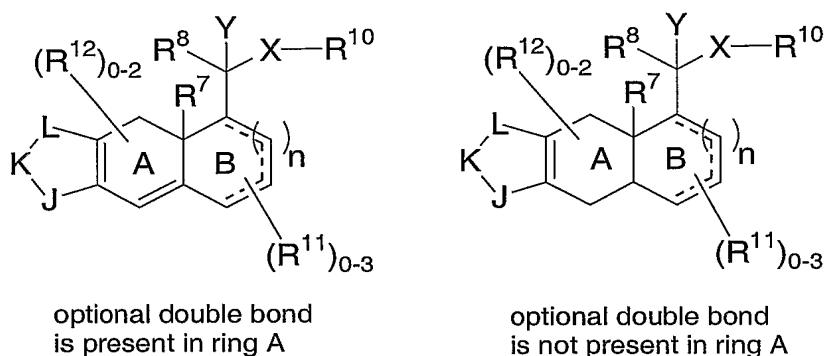
wherein items (2) to (4) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹², N(R¹³)₂ and C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2;

each R¹³ and R¹⁴ is independently selected from the group consisting of hydrogen and C₁₋₄alkyl, optionally substituted from one up to the maximum number of substitutable positions with halo; and

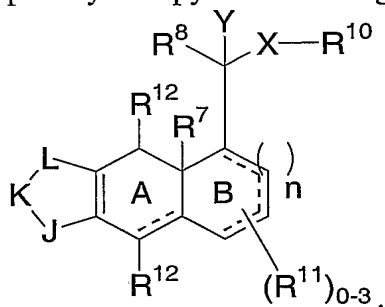
30 each R¹⁵ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, aryl and C₁₋₁₂alkoxycarbonyl, wherein said C₁₋₆alkyl and C₁₋₁₂alkoxycarbonyl are optionally substituted from one up to the maximum number of substitutable positions with halo and said aryl is optionally substituted from one up to

the maximum number of substituable positions with halo and C₁₋₄alkyl, optionally substituted with 1-3 halo groups.

- 5 The optional double bond shown in ring A of the compound of Formula I is depicted as a dotted line and means that the double bond may or may not be present as shown below:

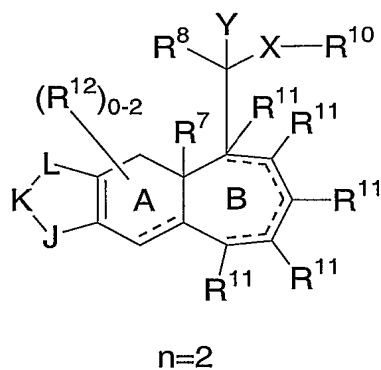
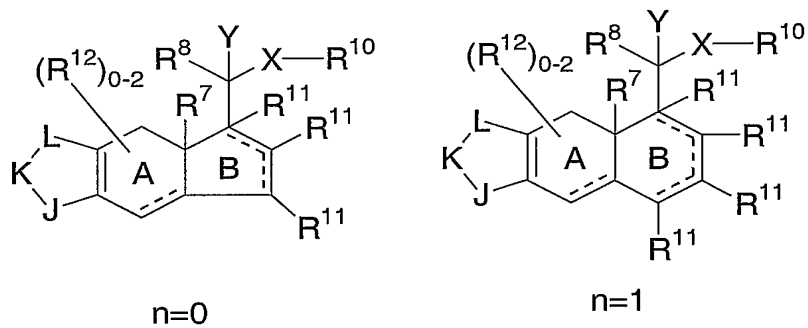


- 10 The substituent R¹² in Formula I may or may not be present. When present, one or two R¹² groups may occupy the following positions:



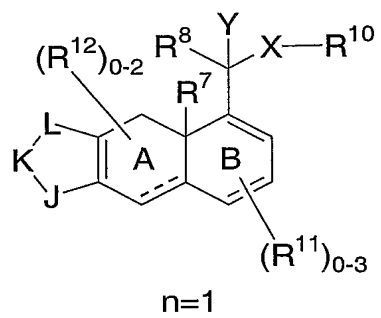
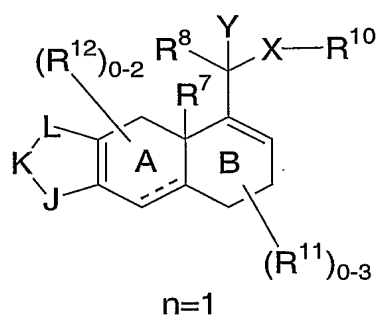
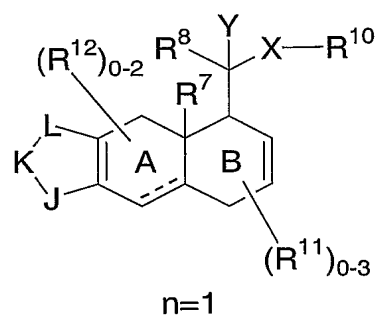
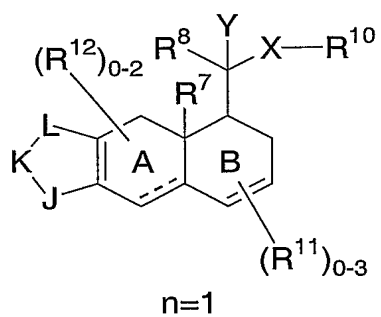
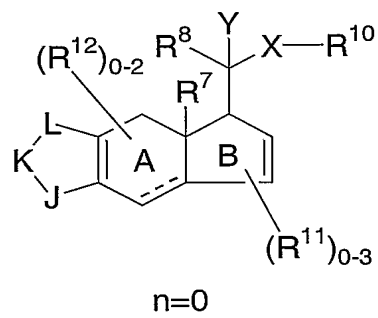
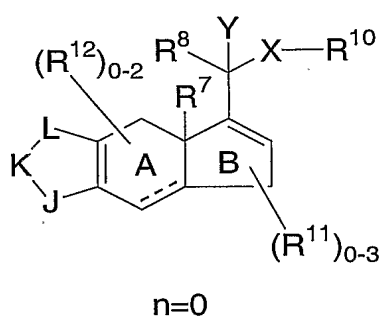
Two R¹² groups may reside on the same carbon atom.

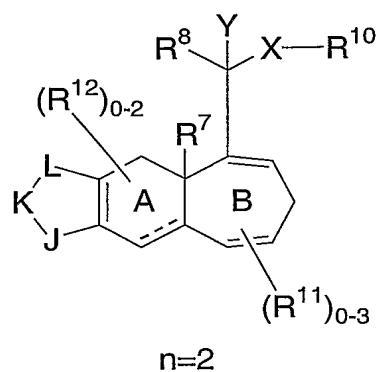
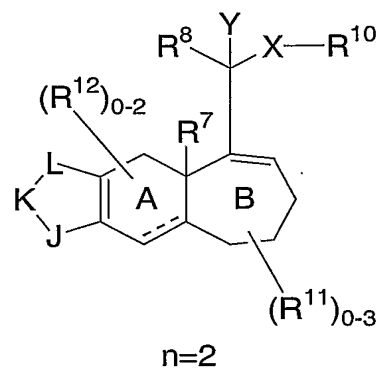
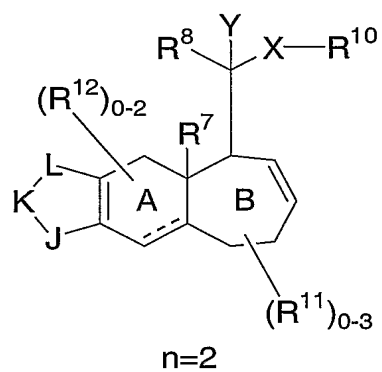
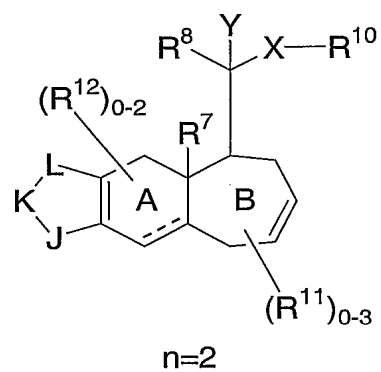
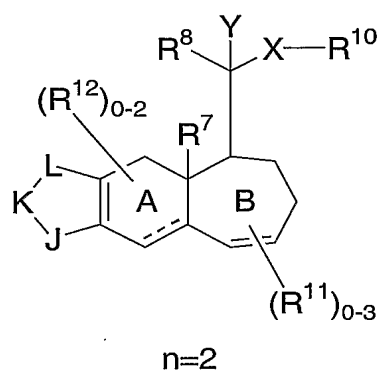
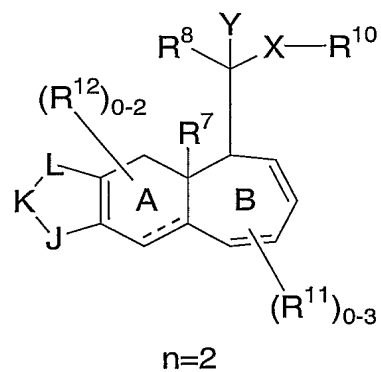
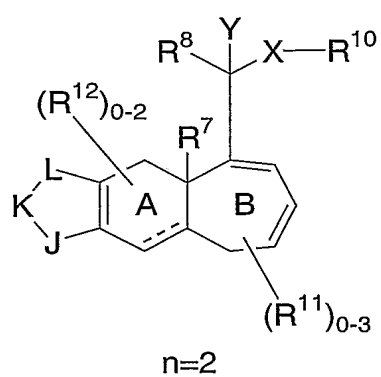
- 15 The substituent R¹¹ in Formula I may or may not be present. When present, one, two or three R¹¹ groups may occupy the following positions:



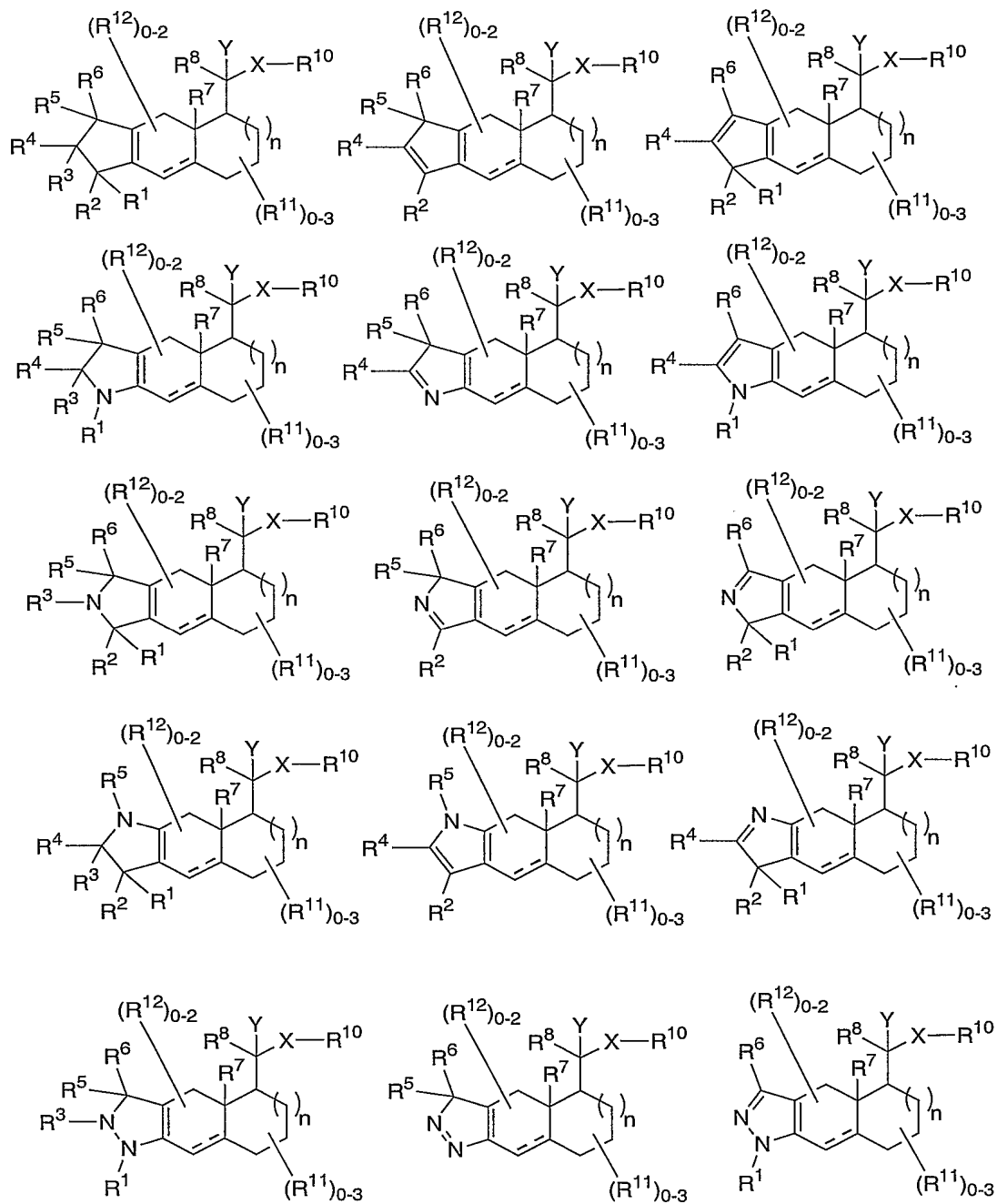
Two R^{11} groups may reside on the same carbon atom.

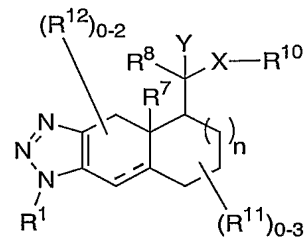
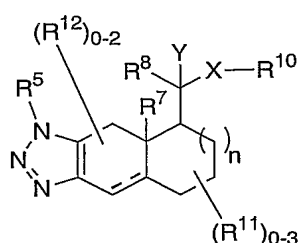
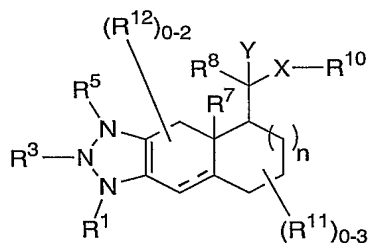
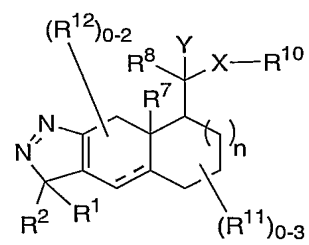
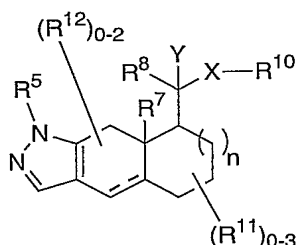
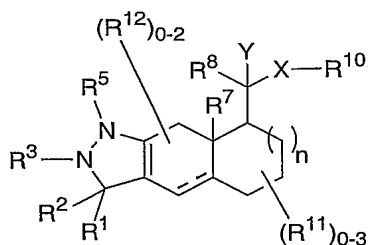
The optional double bonds show in ring B of the compound of Formula I may occupy the following positions:



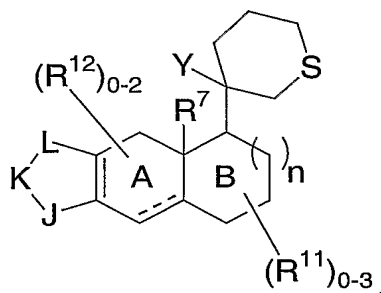
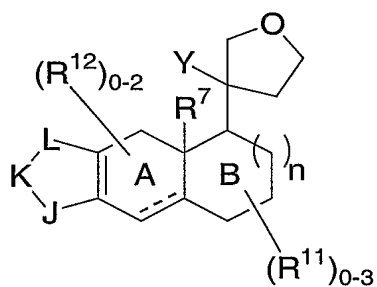
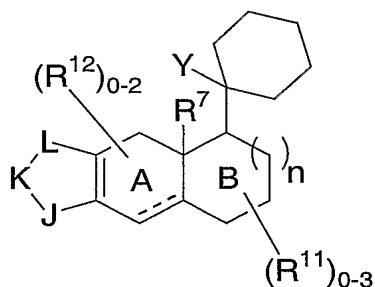
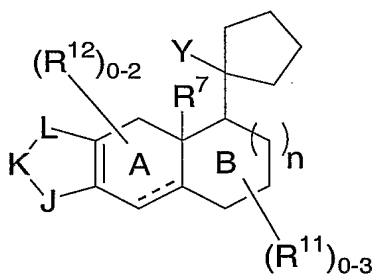
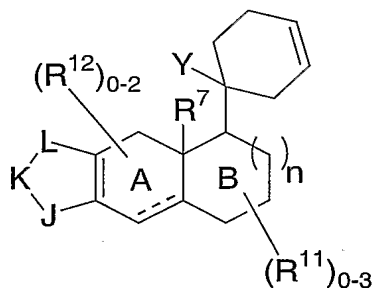
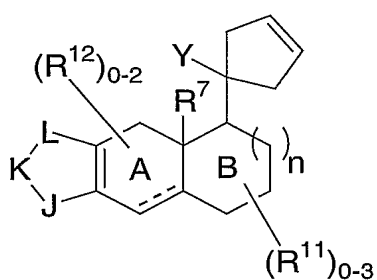


J, K and L as defined in Formula I mean, for example, the following structures:





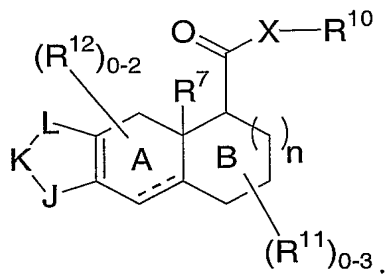
- 5 When X is a bond then R⁸ and R¹⁰ may be joined together to form a 4- to 8-membered monocyclic ring, optionally containing 1-3 heteroatoms selected from O, S and NR¹⁴, and optionally containing 1 or 2 double bonds, which means, for example, the following:



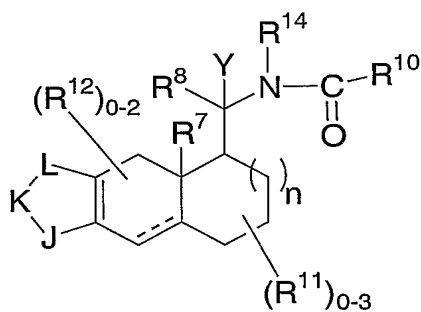
These compounds can be made, for example, by following the procedures outlined in J. Am. Chem. Soc., vol. 118, 100-110, 1996 and J. Am. Chem. Soc., vol. 115, p.9856-9924, 1993, which are hereby incorporated by reference in their entirety.

5

When Y is OR⁹ then R⁸ and R⁹ may be joined together to form a carbonyl group, which means the following:



When X is -N(R¹⁴)-C(O)- the group is attached as follows:



5

Another embodiment of the invention encompasses a compound of Formula I wherein:

10 J is NR¹;

K is NR³;

L is C(R⁵)(R⁶); and

15

R³ and R⁵ are joined together to form a double bond.

Another embodiment of the invention encompasses a compound of
 20 Formula I wherein the optional double bond shown in ring A of the compound of Formula I is present.

Another embodiment of the invention encompasses a compound of Formula I wherein R¹ is aryl or HET, said aryl or HET optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- 5 (a) halo,
- (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl,
- 10 (f) C₃₋₆alkynyl,
- (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (h) aryl,
- (i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
- (j) HET,
- 15 (k) aralkyl,
- (l) aroyl,
- (m) aryloxy,
- (n) aralkoxy and
- (o) CN,

20 wherein items (d) to (g) above and the alkyl portions of item (k) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

25 wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and C₁₋₄alkyl.

30

Within this embodiment of the invention is encompassed a compound of Formula I wherein R¹ is phenyl, optionally substituted with 1-3 halo groups.

Another embodiment of the invention encompasses a compound of Formula I wherein Y is OR⁹. Within this embodiment of the invention is encompassed a compound of Formula I wherein R⁹ is hydrogen.

5 Another embodiment of the invention encompasses a compound of Formula I wherein R⁷ is methyl.

 Another embodiment of the invention encompasses a compound of Formula I wherein R⁸ is hydrogen or methyl.
10

 Another embodiment of the invention encompasses a compound of Formula I wherein X is a bond.

 Another embodiment of the invention encompasses a compound of
15 Formula I wherein R¹⁰ is selected from the group consisting of:

- (1) C₁₋₆alkyl,
- (2) C₂₋₆alkenyl,
- (3) C₃₋₆alkynyl,
- (4) C₃₋₆cycloalkyl,
- 20 (5) C₁₋₆alkoxy,
- (6) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,

wherein items (1) to (6) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂, C₃₋₆cycloalkyl and C₁₋₆alkyl-S(O)_k,
25 wherein k is 0, 1 or 2.

 Another embodiment of the invention encompasses a compound of Formula I wherein R¹⁰ is selected from the group consisting of:

- (1) phenyl
- 30 (2) naphthyl,
- (3) benzyl,
- (4) phenethyl,
- (5) phenoxy,
- (6) benzoyl and
- 35 (7) benzoyloxy,

wherein the aryl portions of items (1) to (7) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- 5 (a) halo,
- (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl,
- (f) C₃₋₆alkynyl,
- 10 (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (h) aryl,
- (i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
- (j) HET,
- (k) aralkyl,
- 15 (l) aroyl,
- (m) aryloxy,
- (n) aralkoxy and
- (o) CN,

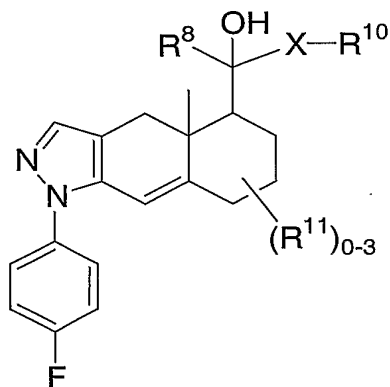
wherein items (d) to (g) above and the alkyl portions of item (k) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and C₁₋₄alkyl.

Another embodiment of the invention encompasses a compound of Formula I wherein R¹⁰ is HET or -C₁₋₄alkyl-HET wherein HET is selected from the group consisting of:

- (1) pyridine,
- (2) thiophene and
- (3) furan,
- 35 or benzofused analogs of (1) to (3) above.

Another embodiment of the invention encompasses a compound of
Formula II:



II

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is a bond;

R^8 and R^{10} are each independently selected from the group consisting
of:

- (1) C_{1-6} alkyl, optionally substituted with hydroxy,
- (2) C_{2-6} alkenyl,
- (3) C_{3-6} alkynyl,
- (4) C_{3-6} cycloalkyl,
- (5) phenyl
- (6) naphthyl,
- (7) benzyl,
- (8) phenethyl and
- (9) pyridine, thiophene or furan, or benzofused analogs thereof,

and R^8 is additionally selected from hydrogen,

wherein items (5), (6) and (9) above and aryl portion of items (7) and (8) above and are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- 5
- (a) halo,
 - (b) hydroxy,
 - (c) methoxy,
 - (d) C₁₋₄alkyl,
 - (e) trifluoromethyl,
 - (f) phenoxy,
 - (g) benzyloxy, optionally substituted with methoxy, and
 - (h) CN;

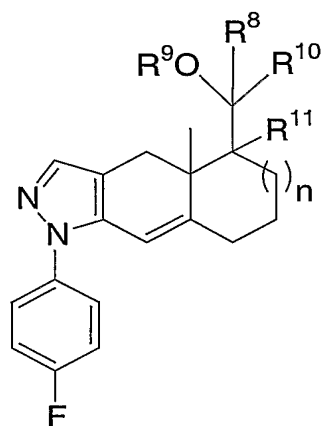
10 each R¹¹ is independently selected from the group consisting of:

- (1) halo,
- (2) methyl and
- (3) hydroxy; and

15 R¹⁴ is independently selected from the group consisting of hydrogen and C₁₋₄alkyl.

Another embodiment of the invention encompasses a compound of Formula II wherein R⁸ is selected from the group consisting of hydrogen or C₁₋₄alkyl.

Another embodiment of the invention encompasses a compound of Formula III:



III

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0 or 1,

R⁸ is hydrogen or methyl,

5

R⁹ is hydrogen or methyl or

R⁸ and R⁹ may be joined together with the oxygen atom shown in Formula III to form a carbonyl group;

10

R¹⁰ is selected from the group consisting of:

- (1) phenyl,
- (2) naphthyl,
- (3) pyridyl,
- 15 (4) furyl or benzofuryl,
- (5) thienyl or benzothienyl, or the S,S-dioxide thereof,
- (6) benzyl,
- (7) quinoline,
- (8) thiazolyl or benzothiazolyl, and
- 20 (9) phenylsulfonylmethyl or phenylsulfonylethyl, wherein

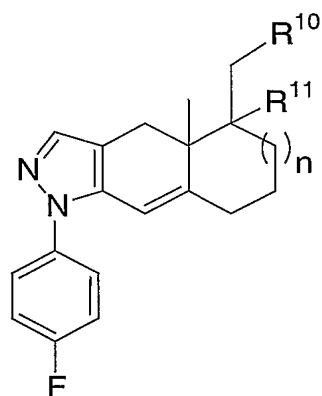
groups (1) to (9) are optionally substituted with 1 to 3 substituents independently selected from the group consisting of:

- 25 (a) halo,
- (b) trifluoromethyl,
- (c) trifluoromethoxy,
- (d) -N(R¹⁴), wherein each R¹⁴ is independently hydrogen or C₁₋₄alkyl,
- 30 (e) pyrrolyl,
- (f) methoxy, ethoxy or isopropoxy, each optionally substituted with a substituent selected from: methoxy, benzyl, cyclopropylmethyl, cyano, methylthio, methylsulfinyl and methylsulfonyl,
- (g) methyl,
- 35 (h) vinyl and

(i) hydroxy, and

R¹¹ is hydrogen or halo.

5 Another embodiment of the invention encompasses a compound of Formula IV:



IV

10 or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0 or 1,

R¹⁰ is selected from the group consisting of:

- 15
- (1) -CH(OR¹³)-aryl, wherein aryl is phenyl or naphthyl,
 - (2) -CH(OR¹³)-HET, and
 - (3) -CH(OR¹³)-C₁₋₄alkyl or -CH(OR¹³)-C₂₋₄alkenyl, said
- CH(OR¹³)-C₁₋₄alkyl or -CH(OR¹³)-C₂₋₄alkenyl optionally substituted with phenylsulfonyl,

20

R¹³ is hydrogen or methyl,

HET is selected from the group consisting of:

- 25
- (1) pyridyl,
 - (2) furyl or benzofuryl,
 - (3) thienyl or benzothienyl, or the S,S-dioxide thereof,
 - (4) benzyl,

- (5) quinoline,
- (6) thiazolyl or benzothiazolyl,

5 said aryl or HET are optionally substituted with 1 to 3 substituents independently selected from the group consisting of:

- (a) halo,
- (b) trifluoromethyl,
- (c) trifluoromethoxy,
- 10 (d) -N(R¹⁴), wherein each R¹⁴ is independently hydrogen or C₁₋₄alkyl,
- (e) pyrrolyl,
- (f) methoxy, ethoxy or isopropoxy, each optionally substituted with a substituent selected from: methoxy, benzyl, cyclopropylmethyl,
- 15 cyano, methylthio, methylsulfinyl and methylsulfonyl,
- (g) methyl,
- (h) vinyl and
- (i) hydroxy, and

20 R¹¹ is hydrogen or halo.

Another embodiment of the invention encompasses a pharmaceutical composition comprising a compound of Formula I in combination with a pharmaceutically acceptable carrier.

25

Another embodiment of the invention encompasses a method for treating a glucocorticoid receptor mediated disease or condition in a mammalian patient in need of such treatment comprising administering the patient a compound of Formula I in an amount that is effective for treating the glucocorticoid receptor mediated disease or condition.

30

Within this embodiment is encompassed the above method wherein the glucocorticoid receptor mediated disease or condition is selected from the group consisting of: tissue rejection, leukemias, lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune

35

proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity, metabolic syndrome, inflammatory bowel disease, systemic lupus erythematosus, polyarthritis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, Human Immunodeficiency Virus (HIV), cell apoptosis, cancer, Kaposi's sarcoma, retinitis pigmentosa, cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, sleep disorders, and anxiety.

Another embodiment of the invention encompasses a method of selectively modulating the activation, repression, agonism and antagonism effects of the glucocorticoid receptor in a mammal comprising administering to the mammal a compound of Formula I in an amount that is effective to modulate the glucocorticoid receptor.

The invention is exemplified by the compounds that follow.

The invention is described using the following definitions unless otherwise indicated.

The term "halogen" or "halo" includes F, Cl, Br, and I.

The term "alkyl" means linear or branched structures and combinations thereof, having the indicated number of carbon atoms. Thus, for example, C₁₋₆alkyl includes methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "alkoxy" means alkoxy groups of a straight, branched or cyclic configuration having the indicated number of carbon atoms. C₁-6alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

5 The term "alkylthio" means alkylthio groups having the indicated number of carbon atoms of a straight, branched or cyclic configuration. C₁-6alkylthio, for example, includes methylthio, propylthio, isopropylthio, and the like.

10 The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C₂-6alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

15 The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. C₃-6alkynyl, for example, includes , propenyl, 1-methylethenyl, butenyl and the like.

20 The term "cycloalkyl" means mono-, bi- or tri-cyclic structures, optionally combined with linear or branched structures, the indicated number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1- bicyclo[4.4.0]decyl, and the like.

The term "aryl" is defined as a mono- or bi-cyclic aromatic ring system and includes, for example, phenyl, naphthyl, and the like.

25 The term "aralkyl" means an alkyl group as defined above of 1 to 6 carbon atoms with an aryl group as defined above substituted for one of the alkyl hydrogen atoms, for example, benzyl and the like.

The term "aryloxy" means an aryl group as defined above attached to a molecule by an oxygen atom (aryl-O) and includes, for example, phenoxy, naphthoxy and the like.

30 The term "aralkoxy" means an aralkyl group as defined above attached to a molecule by an oxygen atom (aralkyl-O) and includes, for example, benzyloxy, and the like.

The term "arylthio" is defined as an aryl group as defined above attached to a molecule by a sulfur atom (aryl-S) and includes, for example, thiophenoxy, thionaphthoxy and the like.

The term "aroyl" means an aryl group as defined above attached to a molecule by an carbonyl group (aryl-C(O)-) and includes, for example, benzoyl, naphthoyl and the like.

5 The term "aroyloxy" means an aroyl group as defined above attached to a molecule by an oxygen atom (aroyl-O) and includes, for example, benzoyloxy or benzoxy, naphthoyloxy and the like.

The term "HET" is defined as a 5- to 10-membered aromatic, partially aromatic or non-aromatic mono- or bicyclic ring, containing 1-4 heteroatoms selected from O, S and N, and optionally substituted with 1-2 oxo groups. Preferably, "HET" is a 5- or 6-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N, for example, pyridine, pyrimidine, pyridazine, furan, thiophene, thiazole, oxazole, isooxazole and the like, or HET is a 9- or 10-membered aromatic or partially aromatic bicyclic ring containing 1-3 heteroatoms selected from O, S, and N, for example, benzofuran, benzothiophene, indole, pyranopyrrole, benzopyran, quionoline, benzocyclohexyl, naphthyridine and the like. "HET" also includes the following: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolyl, furanyl, imidazolyl, indolyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranly, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidyl, methylenedioxybenzoyl, tetrahydrofuranly, and tetrahydrothienyl.

30 For all of the above definitions, each reference to a group is independent of all other references to the same group when referred to in the Specification. For example, if both R¹ and R² are HET, the definitions of HET are independent of each other and R¹ and R² may be different HET groups, for example furan and thiophene.

The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset of the disease or condition or preventing, slowing or reversing the progression of the disease or condition. The term "amount effective for treating" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

The following abbreviations have the indicated meanings:

	AIBN	=	2,2'-azobisisobutyronitrile
	B.P.	=	benzoyl peroxide
15	Bn	=	benzyl
	CCl ₄	=	carbon tetrachloride
	D	=	-O(CH ₂) ₃ O-
	DAST	=	diethylamine sulfur trifluoride
	DCC	=	dicyclohexyl carbodiimide
20	DCI	=	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide
	DEAD	=	diethyl azodicarboxylate
	DIBAL	=	diisobutyl aluminum hydride
	DME	=	ethylene glycol dimethylether
25	DMAP	=	4-(dimethylamino)pyridine
	DMF	=	N,N-dimethylformamide
	DMSO	=	dimethyl sulfoxide
	Et ₃ N	=	triethylamine
	LDA	=	lithium diisopropylamide
30	m-CPBA	=	metachloroperbenzoic acid
	NBS	=	N-bromosuccinimide
	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
35	Ph	=	phenyl

	1,2-Ph	=	1,2-benzenediyl
	Pyr	=	pyridinediyl
	Qn	=	7-chloroquinolin-2-yl
	RS	=	-CH ₂ SCH ₂ CH ₂ Ph
5	r.t.	=	room temperature
	rac.	=	racemic
	THF	=	tetrahydrofuran
	THP	=	tetrahydropyran-2-yl
10	<u>Alkyl group abbreviations</u>		
	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
15	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
	c-Pr	=	cyclopropyl
20	c-Bu	=	cyclobutyl
	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to

salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature and the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to a variety of factors including the age, weight, general health, sex, diet, time of administration, rate of excretion, drug combination and response of the individual patient. In general, the daily dose from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from about 0.5 mg to about 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain from about 1 mg to about 2 g of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

For the treatment of glucocorticoid receptor mediated diseases the compound of Formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, solutions, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate

may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

5 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water-miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

10 Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring
15 phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example
heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial
20 esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose,
25 saccharin or aspartame.

 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening
30 agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in
35 admixture with a dispersing or wetting agent, suspending agent and one or more

preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

5 The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of
10 the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The
15 pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or
20 solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be
25 employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at
30 ambient temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing a compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations

may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The ability of the compounds of Formula I to selectively modulate glucocorticoid receptors makes them useful for treating, preventing or reversing the progression of a variety of inflammatory and autoimmune diseases and conditions. Thus, the compounds of the present invention are useful to treat, prevent or ameliorate the following diseases or conditions: inflammation, tissue rejection, auto-immunity, various malianancies, such as leukemias and lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity and metabolic syndrome.

The compounds of the present invention are also useful for treating, preventing or reversing the progression of disease states involving systemic inflammation such as inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, and cirrhosis.

The compounds of the present invention are useful for treating, preventing or reversing the progression of a variety of topical diseases such as inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, buflous pernphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma.

The compounds of the present invention are also useful in treating, preventing or reversing the progression of disease states associated with Human

Immunodeficiency Virus (HIV), cell apoptosis, and cancer including, but not limited to, Kaposi's sarcoma, immune system activation and modulation, desensitization of inflammatory responses, IL-1 expression, natural killer cell development, lymphocytic leukemia, and treatment of retinitis pigmentosa. Cognitive and behavioral processes are also susceptible to glucocorticoid therapy where antagonists would potentially be useful in the treatment of processes such as cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, stroke, sleep disorders, and anxiety.

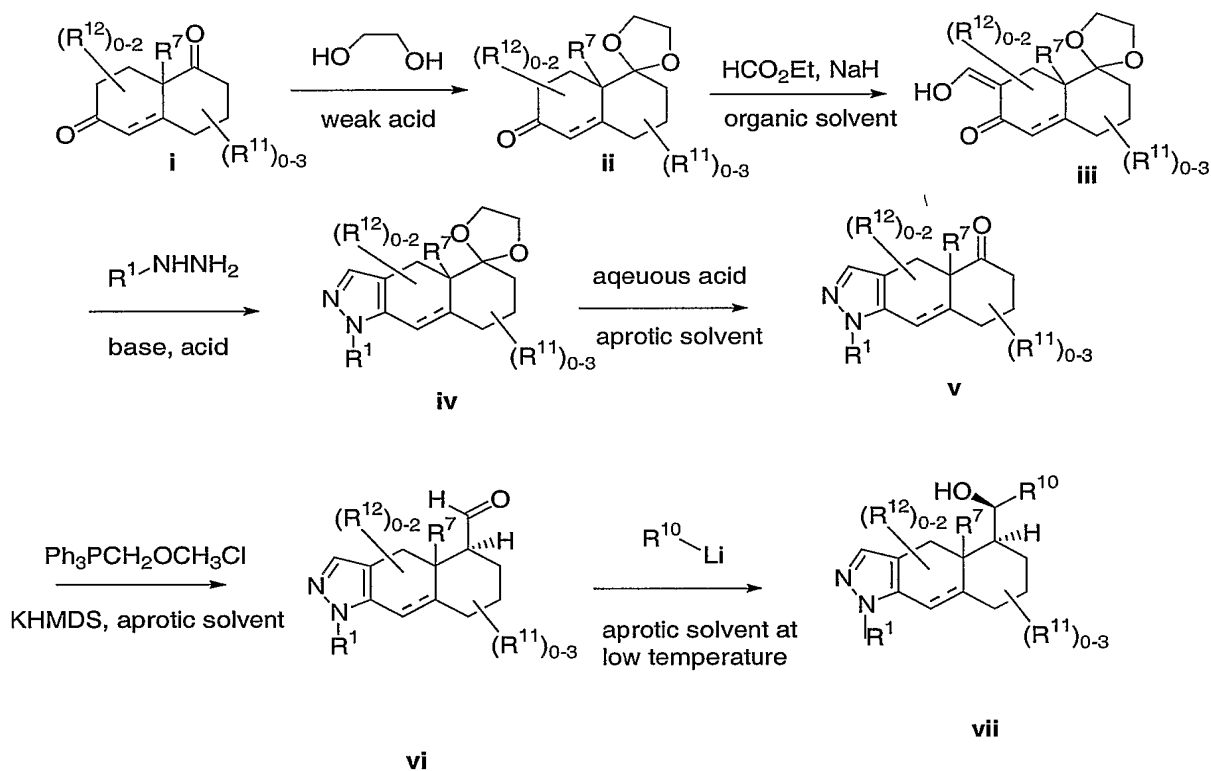
The invention also encompasses a method for treating a glucocorticoid receptor mediated disease comprising concomitantly administering to a patient in need of such treatment a compound of Formula I and one or additional more agents. For treating or preventing asthma or chronic obstructive pulmonary disease, the compounds of Formula I may be combined with one or more agents selected from the group consisting of: β -agonists (e.g., salmeterol), theophylline, anticholinergics (e.g., atropine and ipratropium bromide), cromolyn, nedocromil and leukotriene modifiers (e.g., montelukast). For treating or preventing inflammation, the compounds of Formula I may be combined with one or the following: a salicylate, including acetylsalicylic acid, a non-steroidal antiinflammatory drug, including indomethacin, sulindac, mefenamic, meclofenamic, tolafenamic, tolmetin, ketorolac, diclofenac, ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen and oxaprozin, a TNF inhibitor, including etanercept and infliximab, an IL-1 receptor antagonist, a cytotoxic or immunosuppressive drug, including methotrexate, leflunomide, azathioprine and cyclosporine, a gold compound, hydroxychloroquine or sulfasalazine, penicillamine, darbufelone, and a p38 kinase inhibitor. The compound of Formula I may also be used in combination with bisphosphonates such as alendronate to treat a glucocorticoid mediated disease and simultaneously inhibit osteoclast-mediated bone resorption.

30

METHODS OF SYNTHESIS

Generally, compounds of the present invention may be synthesized by following the following synthetic scheme:

35



- Acid, such as *p*-toluenesulfonic acid, is added to a solution of the
- 5 Wieland-Miescher ketone **i** in ethylene glycol to give ketal **ii**. Ethyl formate and sodium hydride are added to ketal **ii** in an organic solvent such as anhydrous benzene to afford hydroxyketone **iii**. The hydroxyketone **iii** is dissolved in an appropriate acid such as glacial acetic acid and the appropriate hydrazine such as *p*-fluorophenylhydrazine hydrochloride and appropriate base such as sodium acetate
- 10 is added to give pyrazole ketal **iv**. The pyrazole ketal **iv** is dissolved in an aprotic solvent such as THF and an aqueous acid such as aqueous 6N HCl is added to yield the ketone **v**.

- Potassium bis(trimethylsilyl amide) is added to (methoxymethyl)triphenylphosponium chloride in an aprotic solvent such as THF.
- 15 Ketone **v** is added to afford compound **vi**. R¹⁰-Li is added in an aprotic solvent such as THF at low temperature to yield the final product **vii**.

Methods for making compounds of Formula I outside the scope of formula **vii** are easily discernible by those having ordinary skill in the art in view of the above method and the examples set for the below. See, for example, Syth.

Commun., 1994, vol. 24, pp. 279-292; Org. Synth., 1985, vol. 63, pp. 37-43; Org. Synth., 1985, vol. 63, pp. 26-36; and Steroids, 1963, vol. 2, p. 399.

5 The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C,

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature
10 of up to 60°C.,

(iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described;
15 polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;

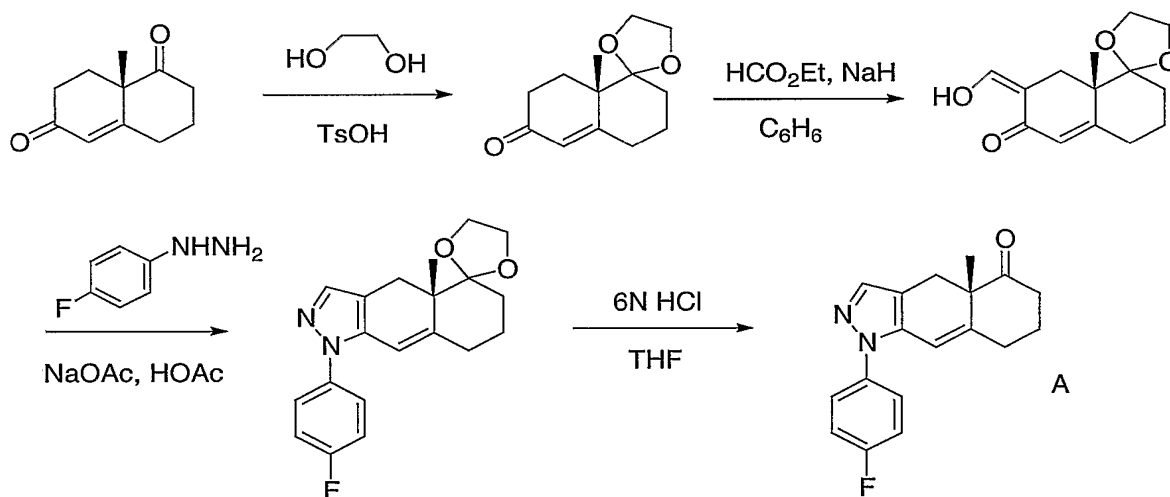
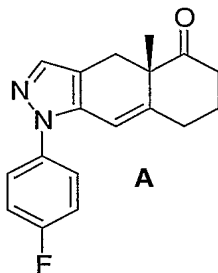
20 (vi) yields are given for illustration only;

(vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 500 MHz or 600 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s.
25 singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (litre(s)), mL (millilitres), g (gram(s)), mg (milligrams(s)), mol
30 (moles), mmol (millimoles), eq (equivalent(s)).

PREPARATIVE EXAMPLES

5

KETONE A

10

Step 1:

15

4 Å molecular sieves (~5 g) and *p*-toluenesulfonic acid (5.34g, 28.05 mmol) were added to a solution of the Wieland-Miescher ketone (5 g, 28.05 mmol) in ethylene glycol (140 mL). After stirring at room temperature for 23 min., the reaction was poured slowly into a 2:1 mixture of ice water/sat. aqueous NaHCO₃ (150 mL). The reaction was extracted with EtOAc (4 x 100 mL) and the

combined organic layers were washed with brine (100 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (0 to 40% EtOAc/hexanes) on silica gel to afford 5.77g (93%) of the ketal as a white solid. LCMS = 223; $(M + 1)^+$. ^1H NMR (CDCl_3 , 500 MHz):
5 δ 5.83 (br d, $J = 1.8$ Hz, 1H), 4.43-3.94 (m, 4H), 2.49-2.40 (m, 3H), 2.39-2.27 (m, 2H), 1.95-1.88 (m, 1H), 1.84-1.78 (m, 1H), 1.76-1.64 (m, 3H), 1.37 (s, 3H).

Step 2:

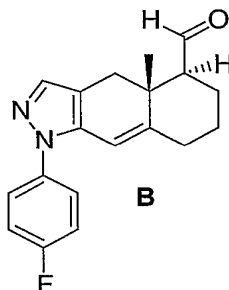
10 Ethyl formate (7.36 mL, 86.48 mmol) and sodium hydride (60% suspension in mineral oil; 3.46 g, 86.48 mmol) were added to a cooled solution (-40°C) of the ketal in anhydrous benzene (200 mL). MeOH (450 μL) was added dropwise over 15 min. and the reaction allowed to warm to room temperature. After stirring for 3 h, the reaction was cooled to 0°C and 50 mL H_2O was added. The biphasic
15 system was shaken and the organic layer was washed with H_2O (3 x 50 mL). The combined aqueous layers were washed with diethyl ether (100 mL) and then acidified to pH 5.5-6 with sat. aqueous KH_2PO_4 . The aqueous layer was extracted with EtOAc (5 x 200 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford 5.04 g (93%) of hydroxyketone product as an
20 orange oil. LCMS = 251; $(M + 1)^+$.

Step 3:

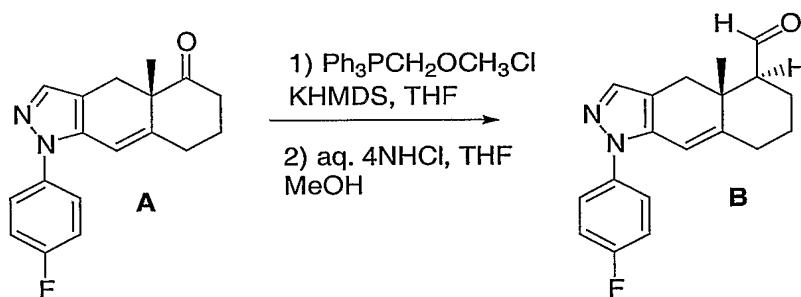
The hydroxyketone (4.1 g, 16.4 mmol) was dissolved in glacial
25 acetic acid (40mL) and *p*-fluorophenylhydrazine hydrochloride (2.8 g, 17.22 mmol) and sodium acetate (1.41 g, 17.22 mmol) were added. After stirring at room temperature for 2 h, the reaction was poured slowly into 10% NaHCO_3 (1 L) and extracted with EtOAc (6 x 500 mL). The combined extracts were washed with brine (500 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude material
30 was purified by flash chromatography (10% EtOAc/hexanes) on silica gel to afford 2.26 g (41%) of the pyrazole ketal as an orange solid. LCMS = 421; $(M + 1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.47-7.44 (m, 2H), 7.43 (s, 1H), 7.18-7.16 (d, $J = 8.5$ Hz, 1H), 7.16-7.14 (d, $J = 8.7$ Hz, 1H), 6.22 (br d, $J = 2.2$ Hz, 1H), 4.11-4.01 (m, 4H), 3.20-3.16 (d, $J = 15.7$ Hz, 1H), 2.54-2.51 (d, $J = 16$ Hz, 1H),
35 2.51-2.40 (m, 1H), 2.34-2.28 (m, 1H), 1.88-1.64 (m, 4H), 1.23 (s, 3H).

Step 4:

The pyrazole ketal (2.26 g; 6.65 mmol) was dissolved in THF (65 mL) and 6N HCl (4.43 mL, 26.6 mL) was added. The reaction was heated at 65 °C for 3.5 h and then poured slowly into 10% NaHCO₃ (150 mL). The mixture was extracted with EtOAc (4 x 250 mL) and the combined extracts washed with brine (2 x 200 mL), dried over MgSO₄ and concentrated *in vacuo* to afford 1.97 g (100%) of Ketone A as a brown oil. LCMS = 297; (M + 1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.50 (s, 1H), 7.49-7.45 (m, 2H), 7.20-7.16 (m, 2H), 6.31 (br d, *J* = 2 Hz, 1 H), 2.96-2.88 (m, 2H), 2.72-2.62 (m, 2H), 2.59-2.53 (m, 2H), 2.14-2.08 (m, 1H), 1.75-1.64 (qt, *J* = 13.1 Hz, *J* = 4.3 Hz, 1H), 1.27 (s, 3H).

ALDEHYDE B

Step 1: Preparation of Aldehyde B



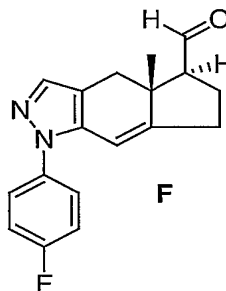
A suspension of (methoxymethyl)triphenylphosponium chloride (4.17 g, 12.16 mmol) in THF (40 mL) was cooled to -40 °C. Potassium bis(trimethylsilyl amide) (20.3 mL of a 0.5 M solution in toluene, 10.15 mmol) was added dropwise by

syringe and the reaction was allowed to warm to 0 °C and held at that temperature for 15 min. A solution of ketone **A** (1.2 g, 4.05 mmol) in THF (12 mL) was added and the reaction was allowed to warm to room temperature. After stirring at room temperature for 24 h, 10 mL of a 1:1 solution of THF/MeOH was added to the
5 reaction followed by 10 mL of 4 N HCl. The reaction became biphasic and stirring was continued at room temperature. After 36 h, the reaction was diluted with EtOAc (300 mL) and washed with H₂O, saturated NaHCO₃, and brine (50 mL each). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue
10 was purified by flash chromatography (5 to 25% EtOAc/hexanes) on silica gel to afford 939.7 mg (75%) of the product **B** as a tan solid; 8:1 (β:α) mixture of aldehyde diastereomers. $R_f = 0.19$ (25% EtOAc/hexanes). LCMS = 311; (M + 1)⁺. ¹H NMR (major isomer) (CDCl₃, 500 MHz) δ 9.91 (d, $J = 1.8$ Hz, 1H), 7.43-7.46 (m, 3H), 7.16 (t, $J = 8.6$ Hz, 2H), 6.17 (d, $J = 1.9$ Hz, 1H), 3.11 (d, $J = 15.6$ Hz, 1H), 2.91 (d, $J = 15.6$ Hz, 1H), 2.32-2.45 (m, 3H), 1.87-1.98 (m, 2H), 1.75 (m, 1H), 1.43 (m, 1H),
15 1.12 (s, 3H).

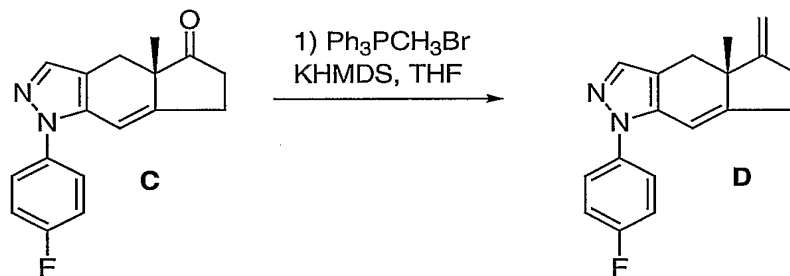
Ketone **C** was prepared in the same manner as ketone **A**.

ALDEHYDE F

20

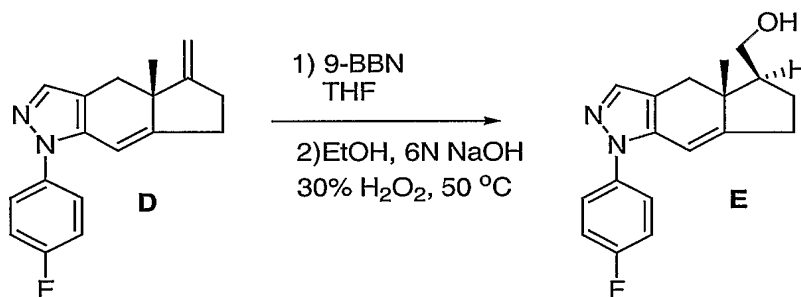


Step 1:



A suspension of methyltriphenylphosphonium bromide (2.05 g, 5.75 mmol) in THF (25 mL) was cooled to -40°C . Potassium bis(trimethylsilyl) amide (9.2 mL of a 0.5 M solution in toluene, 4.6 mmol) was added dropwise by syringe and the reaction was allowed to warm to 0°C and held at that temperature for 15 minutes. Next, a solution of ketone **C** (323.7 mg, 1.15 mmol) in THF (5 mL) was added by cannula. The reaction was allowed to warm to room temperature. After stirring at room temperature for 2 hours, the reaction was filtered through a plug of silica gel with 50% EtOAc/hexanes. The filtrate was concentrated and the residue was purified by flash chromatography with 15% EtOAc/hexanes to afford 265.2 mg (83%) of **D**. $R_f = 0.39$ (25% EtOAc/hexanes). LCMS = 281; $(M + 1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.46-7.49 (m, 2H), 7.44 (s, 1H), 7.13-7.17 (m, 2H), 6.19 (s, 1H), 4.95 (s, 1H), 4.86 (s, 1H), 2.81 (d, $J = 15.3$ Hz, 1H), 2.73 (m, 1H), 2.69 (d, $J = 15.6$ Hz, 1H), 2.54-2.67 (m, 2H), 2.48 (m, 1H), 1.17 (s, 3H).

Step 2:

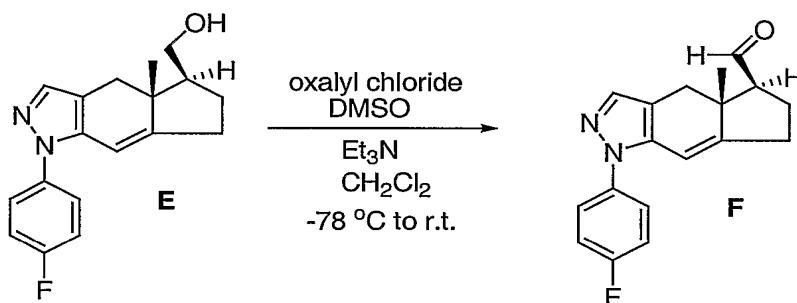


20

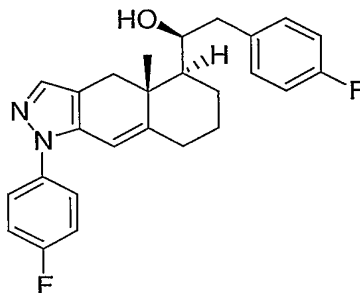
To a solution of **D** (265.2 mg, 0.947 mmol) in THF (17 mL) was added 9-BBN (5.7 mL of a 0.5 M solution in THF, 2.84 mmol). The reaction was stirred at room temperature for 1.5 hours and then cooled to 0°C . EtOH (6.8 mL), 6N NaOH (2.25 mL) and 30% H_2O_2 (1.2 mL) were added, the ice bath was removed, and the

reaction was heated to 50 °C for 1 hour. The reaction was then cooled to room temperature, diluted with EtOAc (100 mL), and washed with H₂O and brine (50 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography with 60% EtOAc/hexanes to afford 282.2 mg (100%) of **E**. *R_f* = 0.19 (55% EtOAc/hexanes). LCMS = 299; (M + 1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.46-7.48 (m, 2H), 7.41 (s, 1H), 7.13-7.16 (m, 2H), 6.14 (s, 1H), 3.81 (dd, *J* = 10.6, 7.1 Hz, 1H), 3.75 (dd, *J* = 10.8, 7.0 Hz, 1H), 2.92 (d, *J* = 15.3 Hz, 1H), 2.66 (d, *J* = 15.3 Hz, 1H), 2.63 (m, 1H), 2.47 (m, 1H), 2.10 (m, 1H), 2.03 (m, 1H), 1.58 (m, 1H), 0.97 (s, 3H).

Step 3:

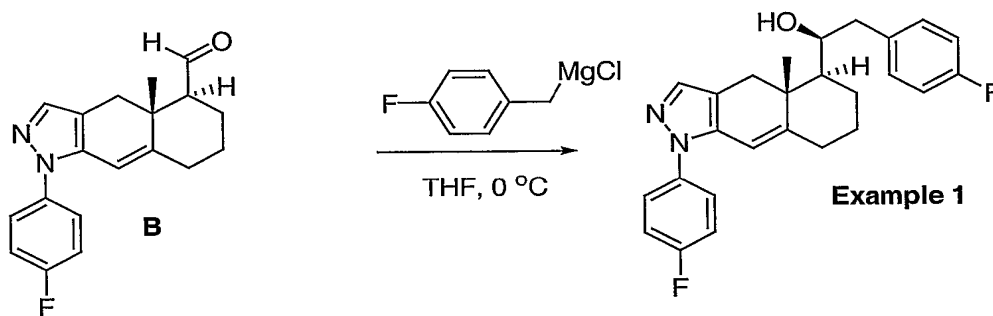


To a solution of oxalyl chloride (46 μL, 0.524 mmol) in CH₂Cl₂ (2 mL) at -78 °C was added DMSO (75 μL, 1.05 mmol) in CH₂Cl₂ (1 mL). The reaction was stirred at -78 °C for 5 minutes and then alcohol **E** (52.1 mg, 0.175 mmol) in CH₂Cl₂ (2 mL) was added. The reaction was stirred for 15 minutes and then Et₃N (295 μL, 2.1 mmol) was added. The reaction was warmed to room temperature, stirred for 20 minutes, and diluted with EtOAc (50 mL). The organic solution was washed with H₂O, saturated NaHCO₃, brine, 1N HCl, saturated NaHCO₃, and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) to afford 41.5 mg (80%) of **F** as a clear oil. *R_f* = 0.27 (40% EtOAc/hexanes). LCMS = 297; (M + 1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 9.89 (d, *J* = 1.6 Hz, 1H), 7.43-7.46 (m, 2H), 7.42 (s, 1H), 7.13-7.16 (m, 2H), 6.17 (s, 1H), 3.01 (d, *J* = 15.4 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H), 2.67-2.75 (m, 2H), 2.51 (m, 1H), 2.56 (m, 1H), 2.06 (m, 1H), 1.06 (s, 3H).

EXAMPLESEXAMPLE 1

5

Step 1: Addition of Aryl Grignard Reagents to Aldehyde **B**



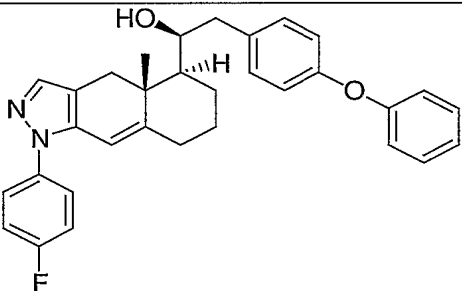
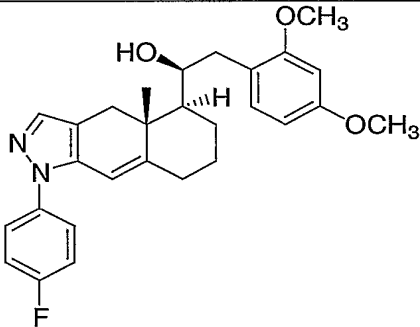
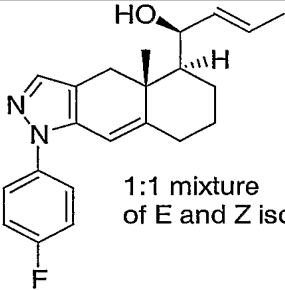
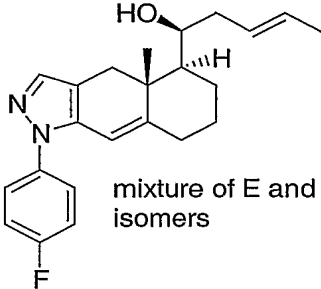
10

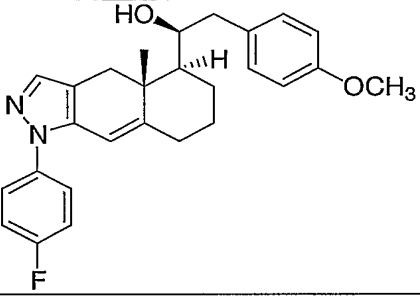
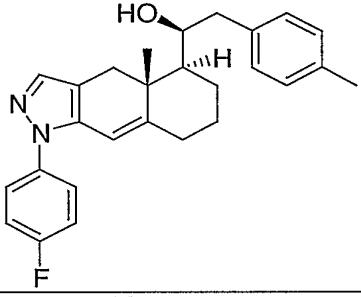
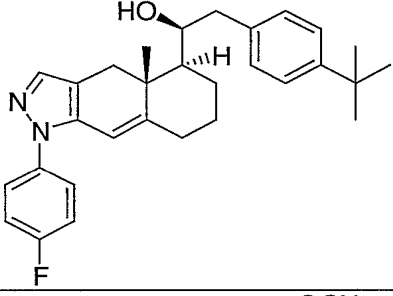
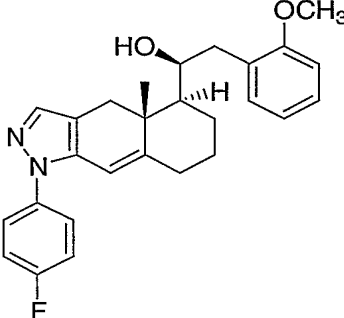
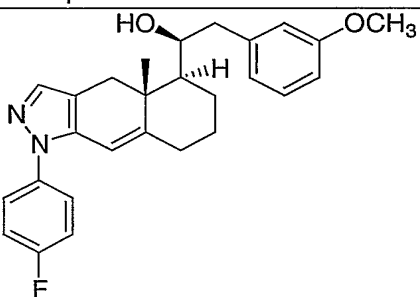
Aldehyde **B** (42.7 mg, 0.138 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. 4-fluorobenzyl magnesium chloride (5.5 mL of a 0.25 M solution in Et₂O, 1.38 mmol) was added dropwise by syringe. The reaction was stirred at 0 °C for 1 h and then quenched with saturated NH₄Cl (25 mL). The mixture was extracted with EtOAc (100 mL) and the organic layer was washed with H₂O and brine (25 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The major product was isolated by flash chromatography (5 to 25% EtOAc/hexanes) to afford 40.6 mg (70%) of Example 1 as a single diastereomer. *R_f* = 0.11 (25% EtOAc/hexanes). LCMS = 421; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.42-7.44 (m, 2H), 7.38 (s, 1H), 7.13-7.20 (m, 4H), 7.02 (t, *J* = 8.6 Hz, 2H), 6.09 (d, *J* = 2.3 Hz, 1H), 4.16 (br s, 1H), 2.85-2.90 (m, 2H), 2.68 (dd, *J* = 13.5, 5.7 Hz, 1H), 2.41 (m, 1H), 2.26-2.32 (m, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 1.71 (qd, *J* = 13.0, 3.3 Hz, 1H), 1.56 (dd, *J* = 12.5, 3.5 Hz, 1H), 1.40 (m, 1H), 1.12 (s, 3H).

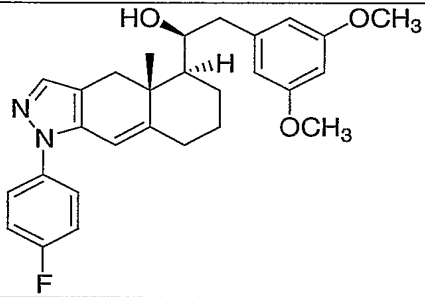
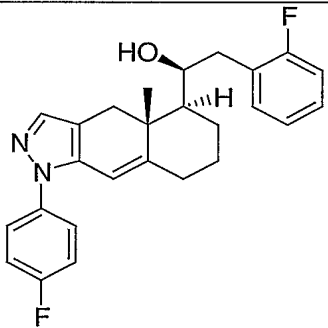
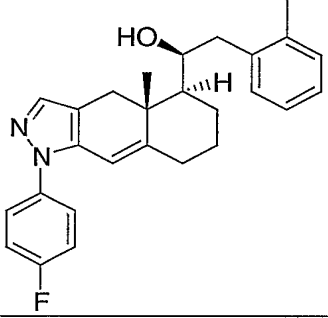
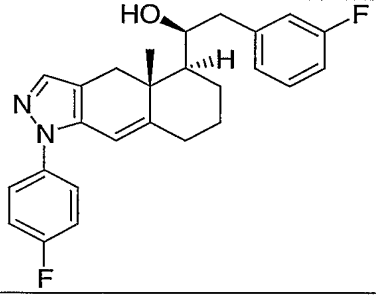
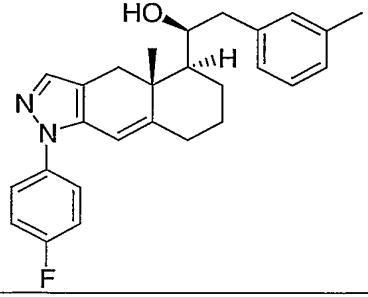
15

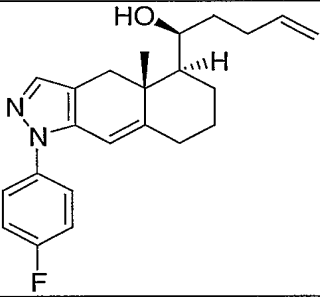
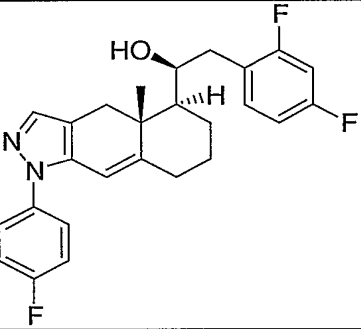
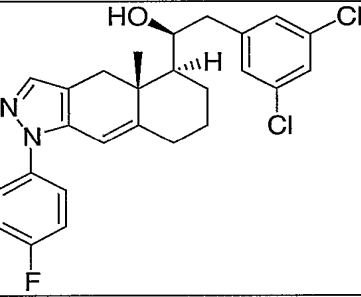
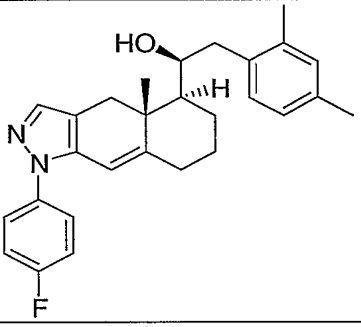
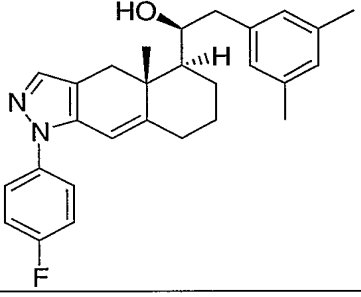
20

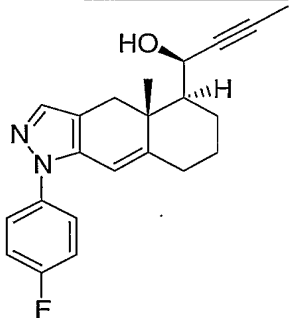
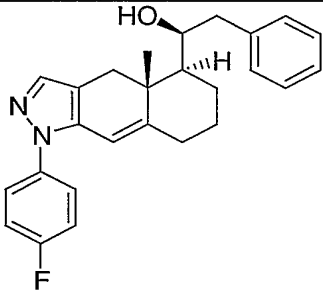
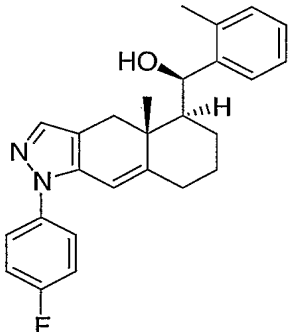
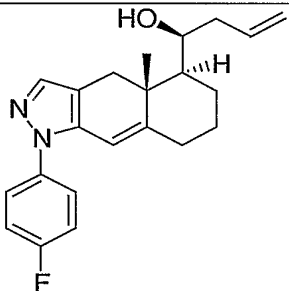
The following compounds are synthesized following procedures analogous to that described in Example 1:

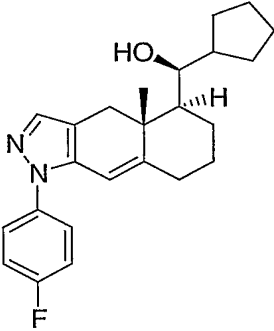
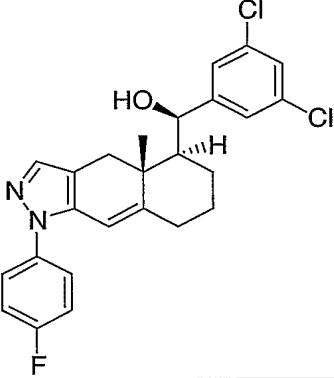
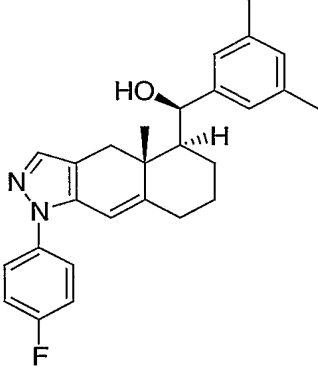
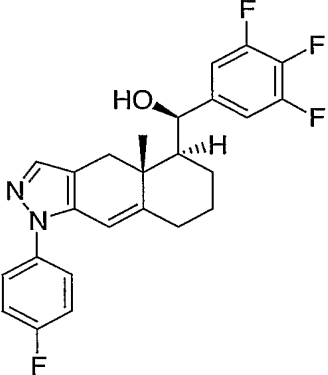
Compound	Molecular structure	LCMS (M+1) ⁺
2		481
3		449
4	 <p>1:1 mixture of E and Z isomers</p>	353
5	 <p>mixture of E and Z isomers</p>	367

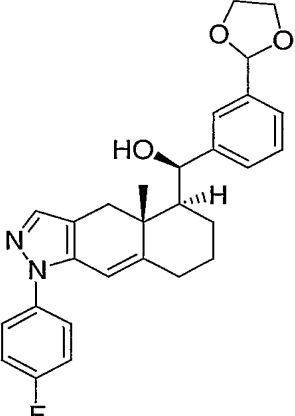
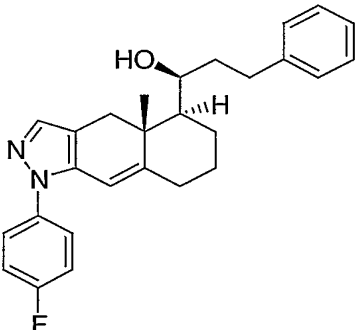
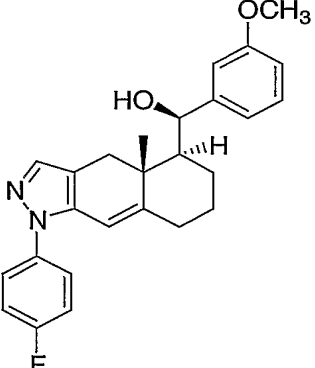
6	 <chem>COc1ccc(cc1)C[C@H](O)[C@@H]2[C@@]3(CC[C@H]4[C@H]2CC=C5[C@@]3(CC[C@@H](C4)N=C5N(c6ccc(F)cc6)C2)C</chem>	433
7	 <chem>Cc1ccc(cc1)C[C@H](O)[C@@H]2[C@@]3(CC[C@H]4[C@H]2CC=C5[C@@]3(CC[C@@H](C4)N=C5N(c6ccc(F)cc6)C2)C</chem>	417
8	 <chem>CC(C)(C)c1ccc(cc1)C[C@H](O)[C@@H]2[C@@]3(CC[C@H]4[C@H]2CC=C5[C@@]3(CC[C@@H](C4)N=C5N(c6ccc(F)cc6)C2)C</chem>	459
9	 <chem>COc1ccc(cc1)C[C@H](O)[C@@H]2[C@@]3(CC[C@H]4[C@H]2CC=C5[C@@]3(CC[C@@H](C4)N=C5N(c6ccc(F)cc6)C2)C</chem>	433
10	 <chem>COc1ccc(cc1)C[C@H](O)[C@@H]2[C@@]3(CC[C@H]4[C@H]2CC=C5[C@@]3(CC[C@@H](C4)N=C5N(c6ccc(F)cc6)C2)C</chem>	433

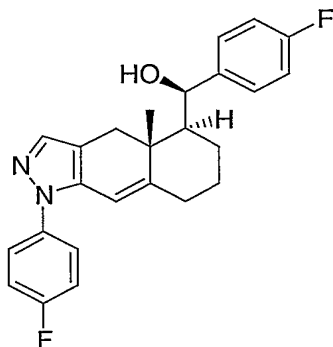
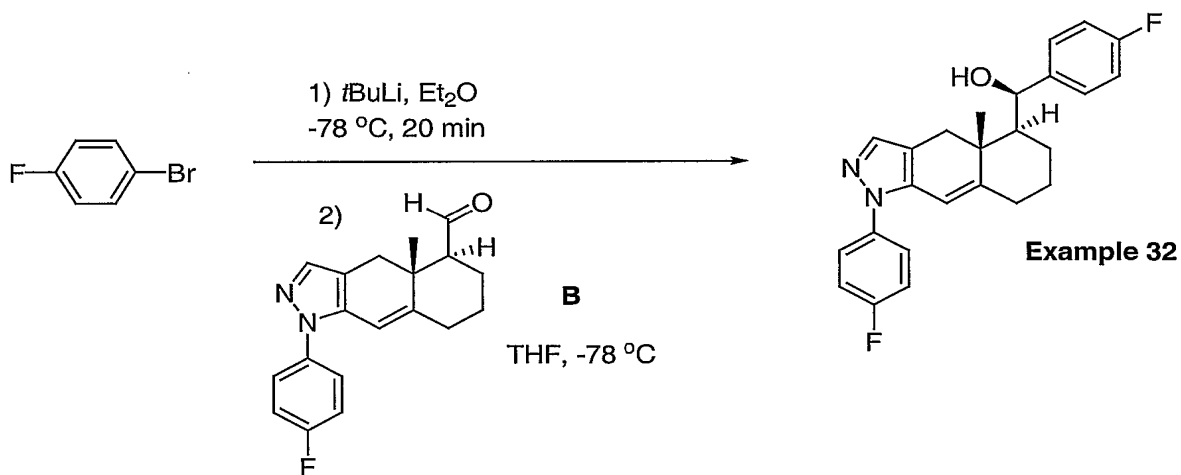
11		463
12		421
13		417
14		421
15		417

16		367
17		439
18		472
19		431
20		431

21		351
22		403
23		403
24		353

25		381
26		457
27		417
28		443

29	 <chem>Fc1ccc(cc1)-n2c3c(cc4c3ccc5c4CCCC5C2)C[C@H](C)[C@H](C1=CC=C(C=C1)C2=CCOC2)O</chem>	461
30	 <chem>Fc1ccc(cc1)-n2c3c(cc4c3ccc5c4CCCC5C2)C[C@H](C)[C@H](CCOCC1=CC=CC=C1)O</chem>	417
31	 <chem>COc1ccc(cc1)[C@H](O)[C@H](C2=CC=CC=C2)[C@@H](C)C3=C(C=C4C(=C3)C(=CC5=C4N=CN5C6=CC=C(C=C6)F)N)C</chem>	419

EXAMPLE 325 Step 1: Addition of Aryl or Vinyl Lithium Reagents to Aldehyde **B**

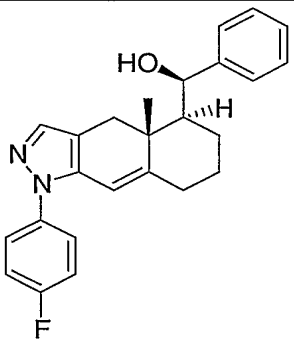
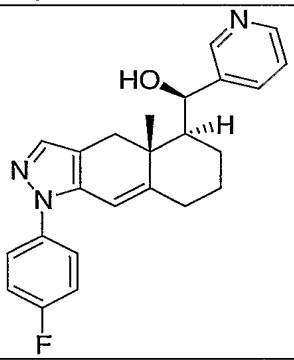
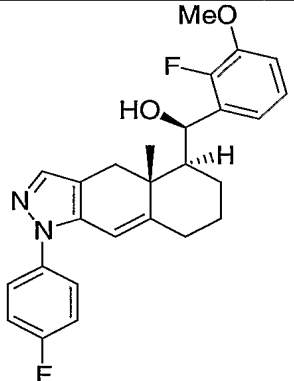
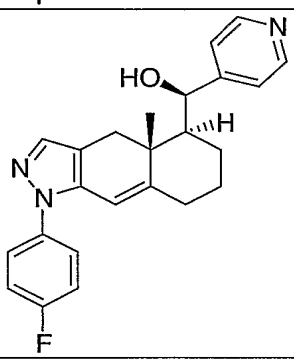
10 A solution of 1-bromo-4-fluorobenzene (176 μ L, 1.6 mmol) in Et₂O (16 mL) was cooled to -78 °C and *t*BuLi (1.9 mL of a 1.7 M solution in pentanes, 3.2 mmol) was added dropwise by syringe. The reaction was stirred at -78 °C for 20 min. and then aldehyde **B** (49.6 mg, 0.16 mmol) in THF (4 mL) was added by cannula. The reaction was stirred at -78 °C for 45 min. 1 mL of isopropyl alcohol was added

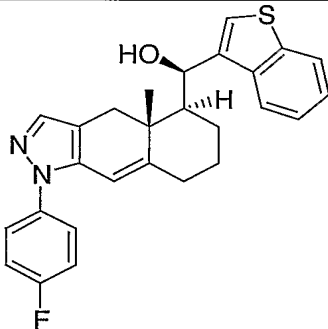
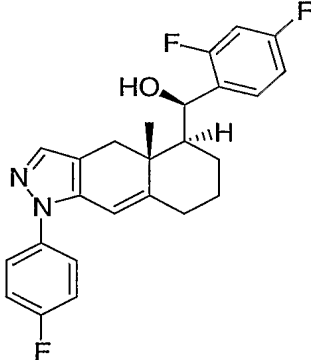
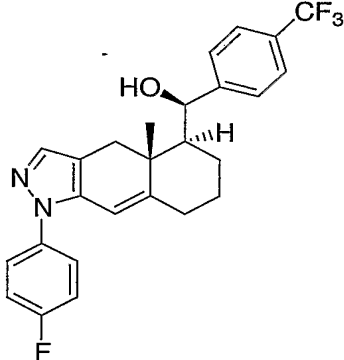
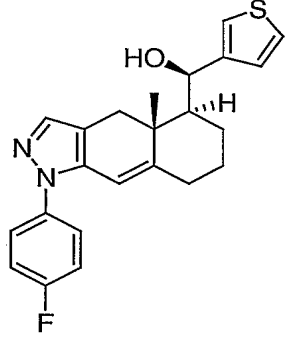
15 at -78 °C and the reaction was poured into saturated NH₄Cl. The mixture was extracted with EtOAc (100 mL) and the organic layer was washed with water and brine (25 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 20% EtOAc/hexanes) gave 52.8 mg of Example **32** contaminated with minor

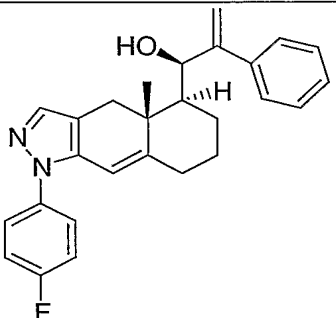
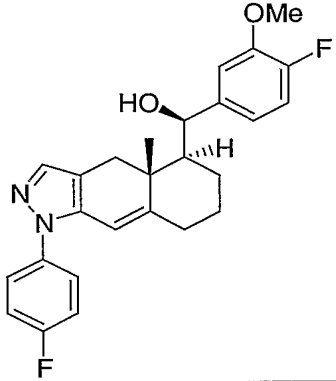
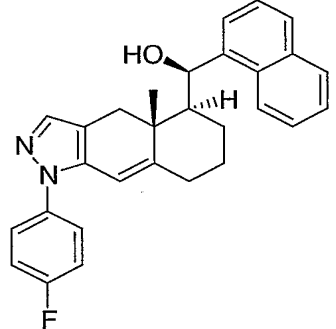
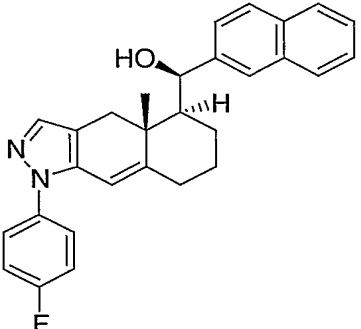
diastereomers. Further purification by chiral HPLC (AD column, 20% isopropyl alcohol/heptanes) gave 35.6 mg (55%) of pure Example 32. $R_f = 0.16$ (25% EtOAc/hexanes). LCMS = 407; $(M+1)^+$. 1H NMR ($CDCl_3$, 500 MHz): δ 7.45 (m, 4H), 7.32 (dd, $J = 9.5, 5.0$ Hz, 2H), 7.15 (t, $J = 8.5$ Hz, 2H), 7.04 (t, $J = 8.8$ Hz, 2H), 6.12 (d, $J = 2.1$ Hz, 1H), 5.18 (s, 1H), 3.18 (d, $J = 15.1$ Hz, 1H), 2.75 (d, $J = 15.1$ Hz, 1H), 2.41 (m, 1H), 2.28 (bd, $J = 15.1$ Hz, 1H), 1.82 (m, 1H), 1.66-1.71 (m, 2H), 1.58 (m, 1H), 1.26 (s, 3H), 1.20 (m, 1H).

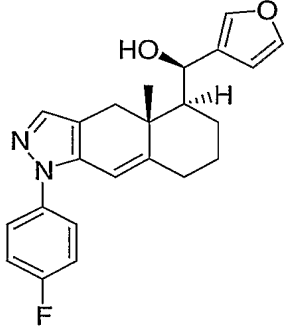
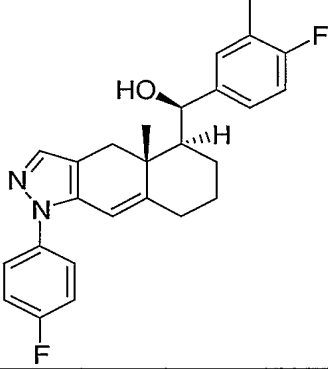
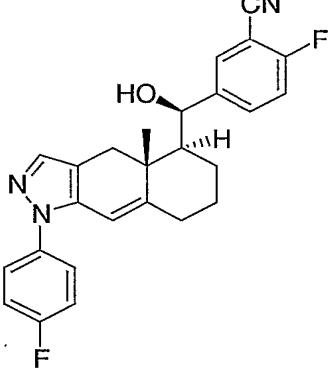
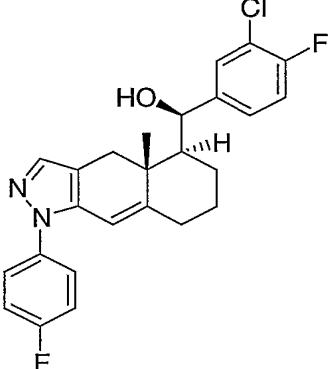
The following compounds were synthesized following procedures analogous to that described in Example 32:

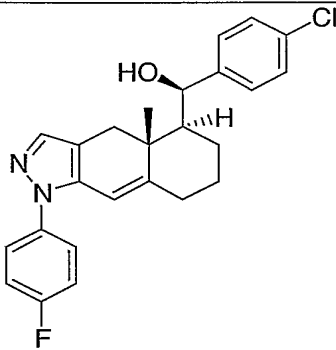
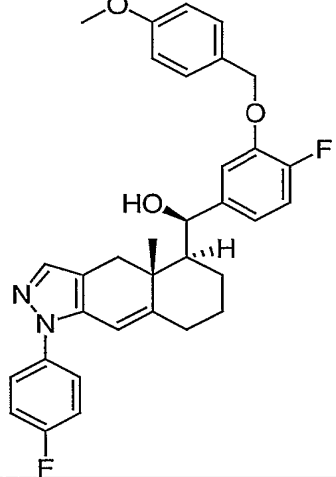
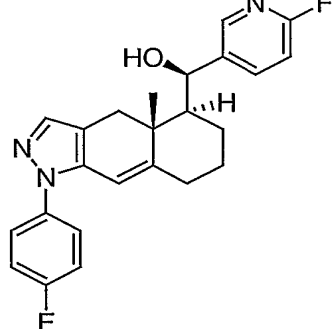
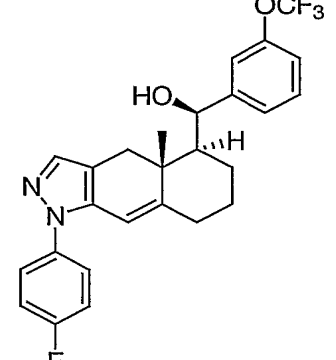
Compound	Molecular structure	LCMS $(M+1)^+$
33		407
34		390

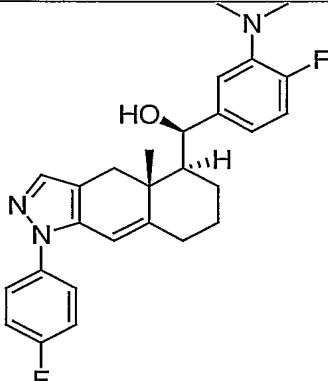
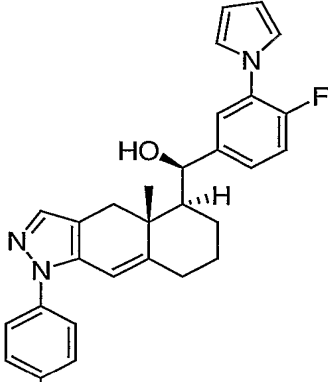
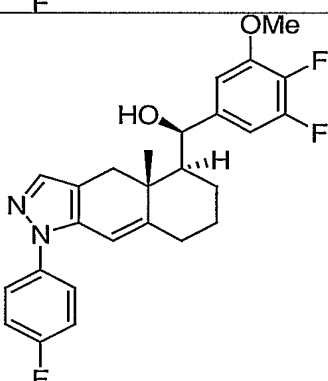
35		389
36		390
37		437
38		390

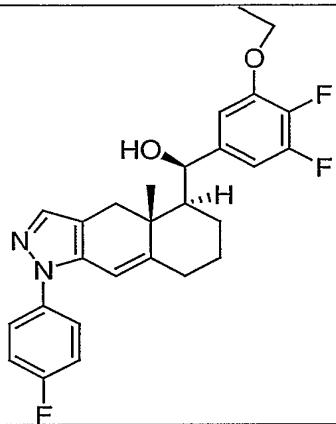
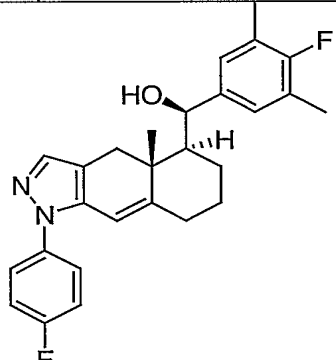
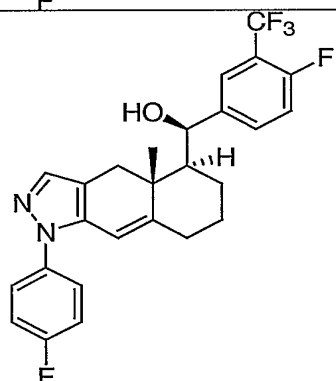
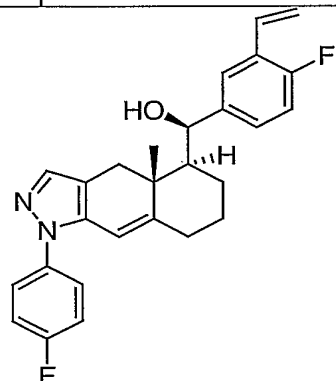
39	 <chem>O[C@H](c1ccc2c(c1)sc2)[C@@H](C3=C4C(=C(C=C3)C(=C5C(=C4)C(=C(C=C5)N6C(=N6)N(C7=CC=CC=C7)F)C8=CC=CC=C8)C=C4)C=C5</chem>	445
40	 <chem>O[C@H](c1cc(F)c(F)cc1)[C@@H](C2=C3C(=C(C=C2)C(=C4C(=C3)C(=C(C=C4)N5C(=N5)N(C6=CC=CC=C6)F)C7=CC=CC=C7)C=C3)C=C4</chem>	425
41	 <chem>O[C@H](c1ccc(C(F)(F)F)cc1)[C@@H](C2=C3C(=C(C=C2)C(=C4C(=C3)C(=C(C=C4)N5C(=N5)N(C6=CC=CC=C6)F)C7=CC=CC=C7)C=C3)C=C4</chem>	457
42	 <chem>O[C@H](c1ccsc1)[C@@H](C2=C3C(=C(C=C2)C(=C4C(=C3)C(=C(C=C4)N5C(=N5)N(C6=CC=CC=C6)F)C7=CC=CC=C7)C=C3)C=C4</chem>	395

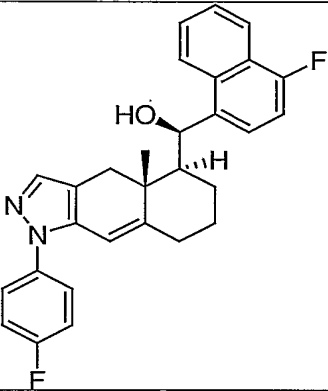
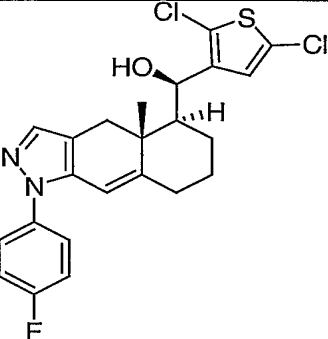
43		415
44		437
45		439
46		439

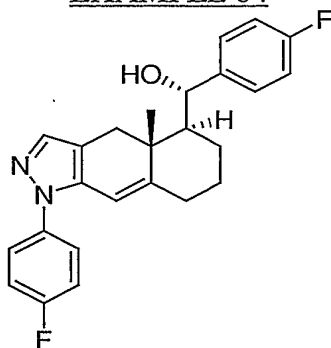
47		379
48		421
49		433
50		441

51		423
52		543
53		408
54		473

55		450
56		472
57		455

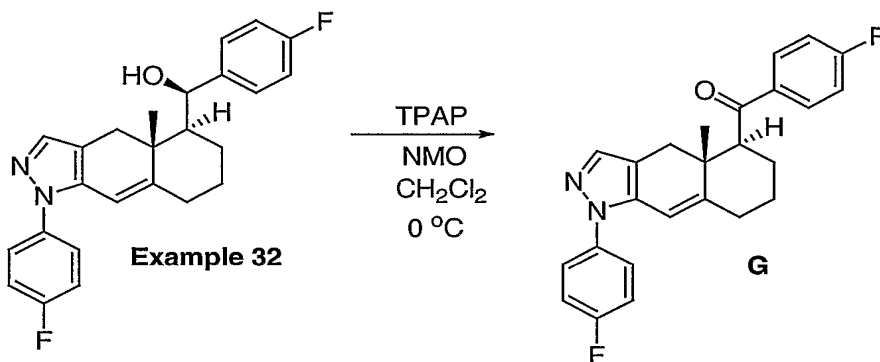
58		469
59		435
60		475
61		433

62		457
63		463

EXAMPLE 64

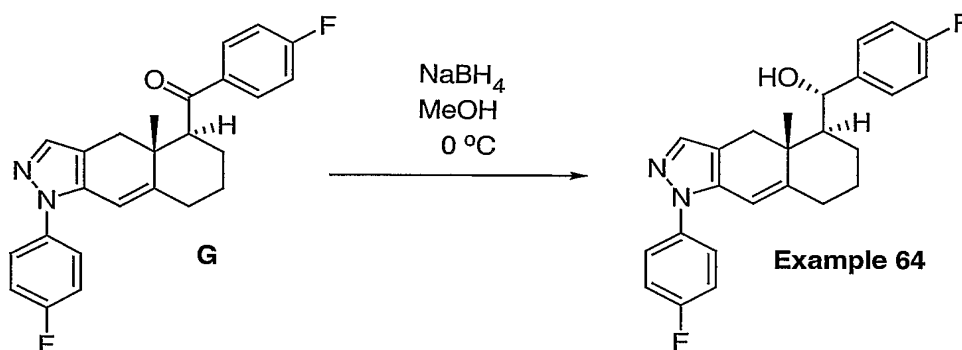
Step 1: Oxidation to the ketone.

5



10 A solution of **Example 32** (23.0 mg, 0.057 mmol) in CH_2Cl_2 (2 mL) was cooled to 0°C and NMO (10 mg, 0.085 mmol) was added. After 5 minutes, TPAP (2 mg, 0.0057 mmol) was added to the reaction. The reaction was stirred at 0°C for 3 hours and then loaded directly onto a column of silica gel. Elution with 100% CH_2Cl_2 followed by 25% EtOAc/hexanes afforded 19.2 mg (84%) of product **G**. $R_f = 0.32$ (25% EtOAc/hexanes). LCMS = 405; $(M+1)^+$.

Step 2: Reduction of ketone.



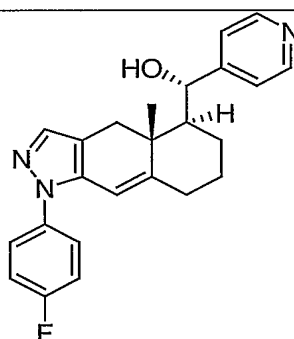
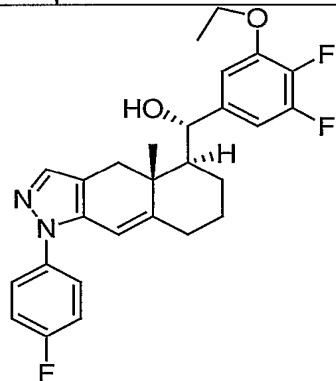
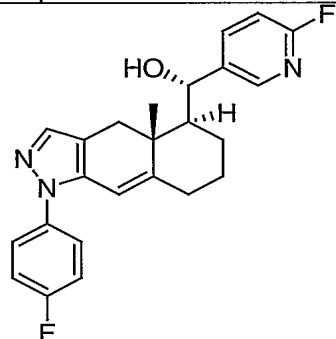
5

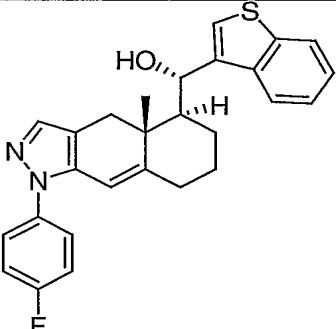
Compound **G** (19.2 mg, 0.048 mmol) was dissolved in MeOH (2 mL) and cooled to 0 °C. NaBH₄ (10 mg 0.238 mmol) was added. The reaction was stirred at 0 °C for 15 min. and then quenched with saturated NH₄Cl (5 mL). The mixture was extracted with EtOAc (30 mL). The organic layer was washed with H₂O and brine (10 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes) followed by chiral HPLC to remove minor impurities (AD column, 12% IPA/hexanes) to give 12.6 mg (65%) of pure **Example 64**. *R_f* = 0.16 (25% EtOAc/heptanes). LCMS = 407; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 7.45 (dd, *J* = 9.0, 4.8 Hz, 2H), 7.40 (s, 1H), 7.32 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.14 (t, *J* = 8.4 Hz, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.15 (s, 1H), 4.64 (d, *J* = 9.0 Hz, 1H), 3.63 (d, *J* = 16.2 Hz, 1H), 2.78 (d, *J* = 16.2 Hz, 1H), 2.27-2.29 (m, 2H), 2.07 (bs, 1H), 1.89 (m, 1H), 1.68 (m, 1H), 1.05-1.25 (m, 2H), 1.13 (s, 3H).

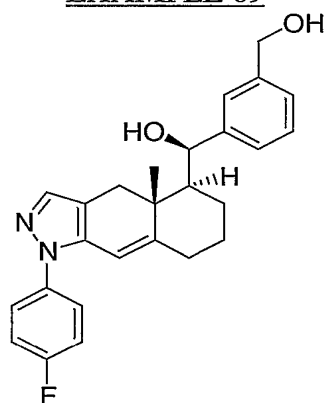
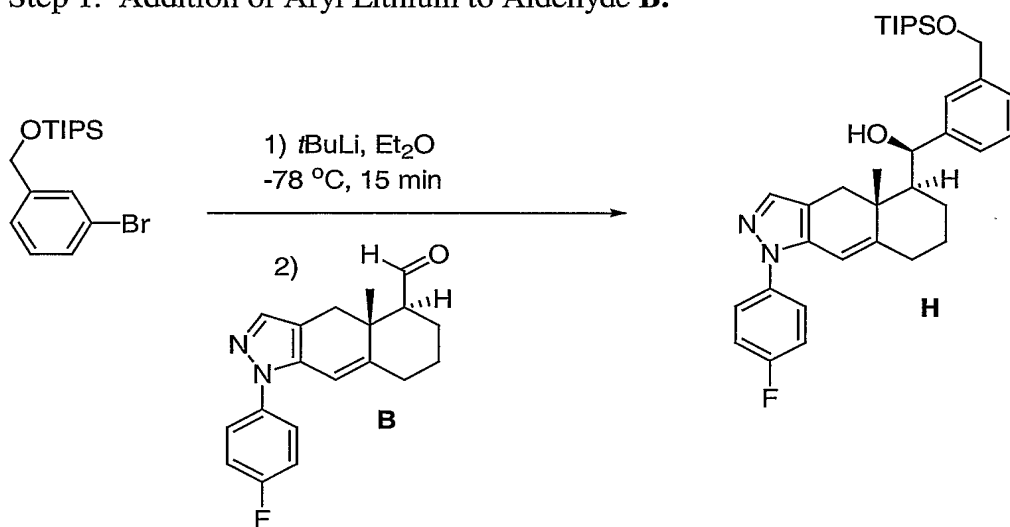
10

15

The following examples were synthesized following a procedure analogous to that described in Example 64:

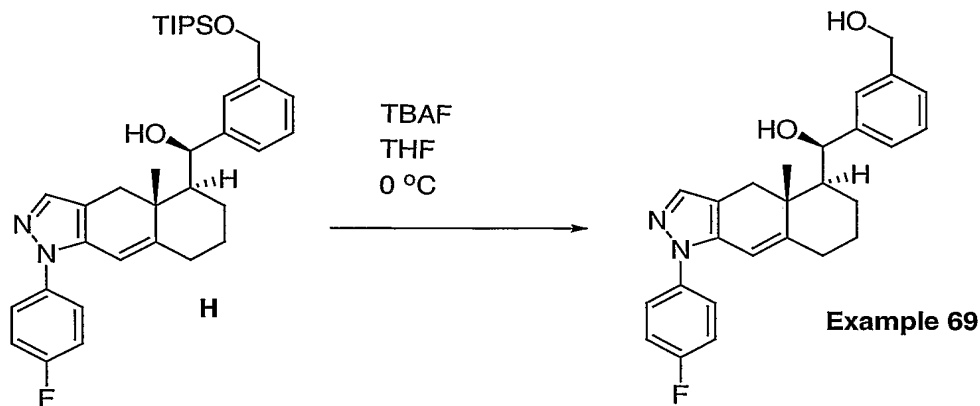
Compound	Molecular structure	LCMS (M+1) ⁺
65		390
66		369
67		408

68		445
----	--	-----

EXAMPLE 695 Step 1: Addition of Aryl Lithium to Aldehyde **B**.

A solution of O-triisopropylsilyloxy-3-bromobenzyl alcohol (230 mg, 0.67 mmol) in Et₂O (6.5 mL) was cooled to -78 °C and *t*-BuLi (785 μL of a 1.7 M solution in pentanes, 1.34 mmol) was added. The reaction was stirred at -78 °C for 15 min. Aldehyde **B** (20.7 mg, 0.067 mmol) was added by cannula as a solution in THF (2 mL). The reaction was stirred at -78 °C for 30 min. 1 mL of isopropyl alcohol was added and the reaction was poured into saturated NH₄Cl (15 mL). The mixture was extracted with EtOAc (50 mL). The organic layer was washed with H₂O and brine (15 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 5 to 15% EtOAc/hexanes) to give 32.4 mg of product containing 1 major and 2 minor diastereomers. Further purification by chiral HPLC (AD column, 15% IPA/heptanes) afforded 19.4 mg (51%) of pure **H** (major diastereomer). *R*_f = 0.22 (25% EtOAc/hexanes). LCMS = 575; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.45-7.48 (m, 3H), 7.36 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 6.8 Hz, 2H), 7.13-7.17 (m, 2H), 6.11 (d, *J* = 2.0 Hz, 1H), 5.19 (s, 1H), 4.86 (s, 2H), 3.19 (d, *J* = 15.1 Hz, 1H), 2.76 (d, *J* = 15.1 Hz, 1H), 2.41 (m, 1H), 2.27 (br d, *J* = 15.1 Hz, 1H), 1.63-1.82 (m, 5H), 1.27 (s, 3H), 1.15-1.22 (m, 3H), 1.10 (d, *J* = 6.9 Hz, 18H).

Step 2: Desilylation of the Protected Alcohol or Phenol

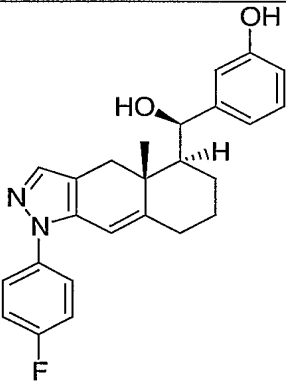
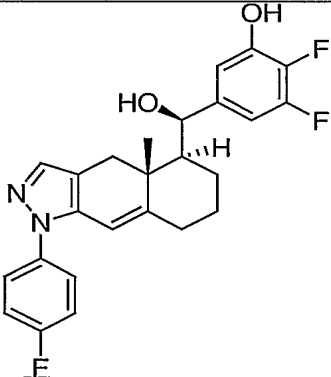


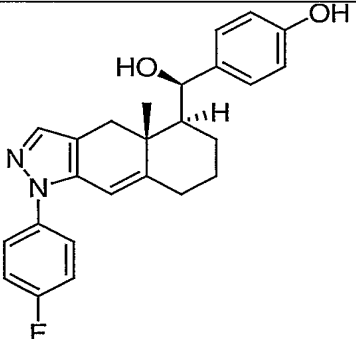
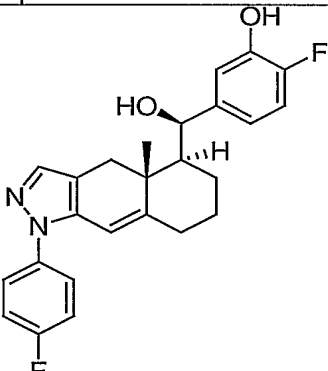
Compound **H** (19.4 mg, 0.034 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. TBAF (169 µL of a 1 M solution in THF, 0.169 mmol) was added. The reaction was stirred at 0 °C for 20 min. and then quenched with saturated NH₄Cl (5 mL). The mixture was extracted with EtOAc (30 mL). The organic layer was washed with H₂O and brine (10 mL each), dried over Na₂SO₄, filtered, and

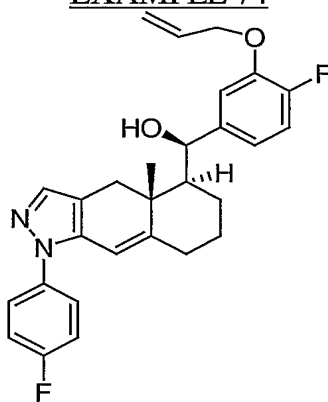
concentrated *in vacuo*. The residue was purified by flash chromatography (75% EtOAc/hexanes) to give 12.9 mg (91%) of pure **Example 69**. $R_f = 0.28$ (75% EtOAc/hexanes). LCMS = 419; $(M+1)^+$. ^1H NMR (DMSO, 500 MHz): δ 7.50-7.53 (m, 3H), 7.34 (t, $J = 8.8$ Hz, 2H), 7.29 (s, 1H), 7.25 (t, $J = 7.4$ Hz, 1H), 7.21 (d, $J = 7.6$ Hz, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 6.17 (s, 1H), 5.12 (t, $J = 5.8$ Hz, 1H), 4.99-5.03 (m, 2H), 4.48 (d, $J = 5.7$ Hz, 2H), 3.19 (d, $J = 15.3$ Hz, 1H), 2.73 (d, $J = 15.3$ Hz, 1H), 2.26-2.36 (m, 2H), 1.63-1.71 (m, 2H), 1.53 (d, $J = 11.2$ Hz, 1H), 1.38 (d, $J = 12.8$ Hz, 1H), 1.17 (s, 3H), 1.03 (m, 1H).

10

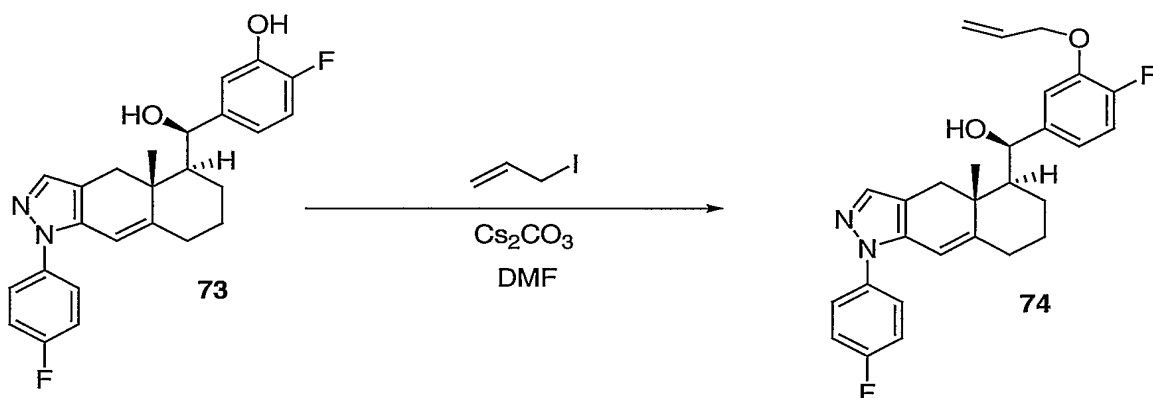
The following examples were synthesized following a procedure analogous to that described in Example 69:

Compound	Molecular structure	LCMS $(M+1)^+$
70		405
71		441

72		405
73		405

EXAMPLE 74

Step 1: Alkylation of Example 73.



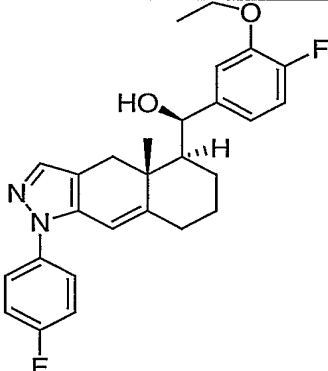
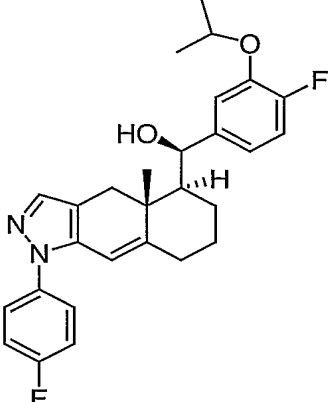
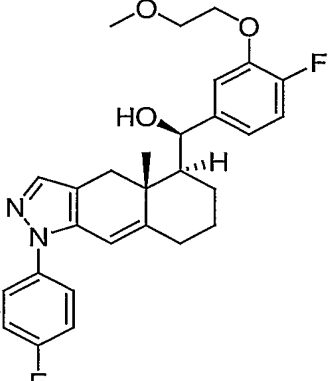
5

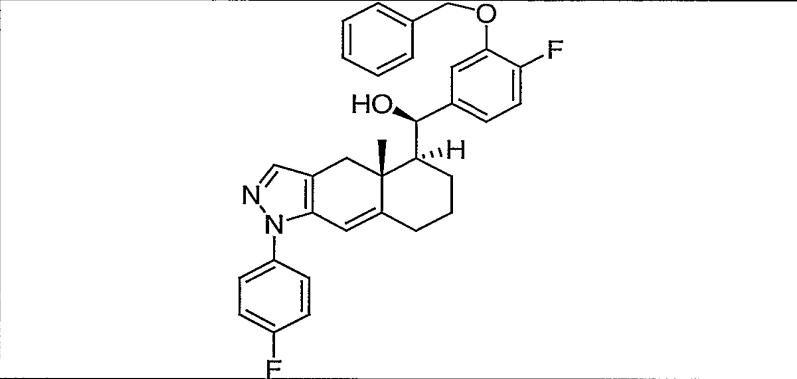
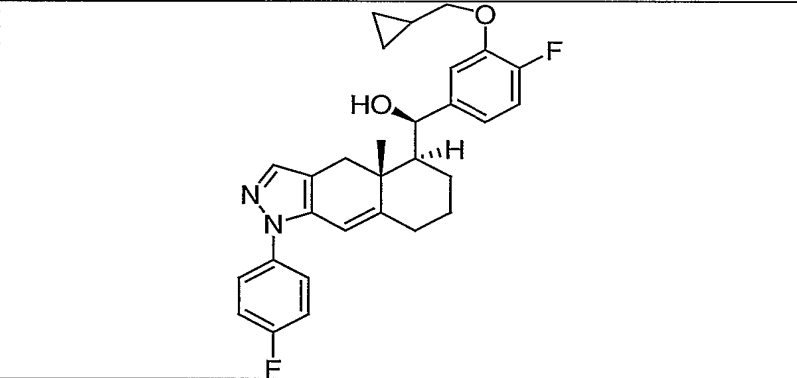
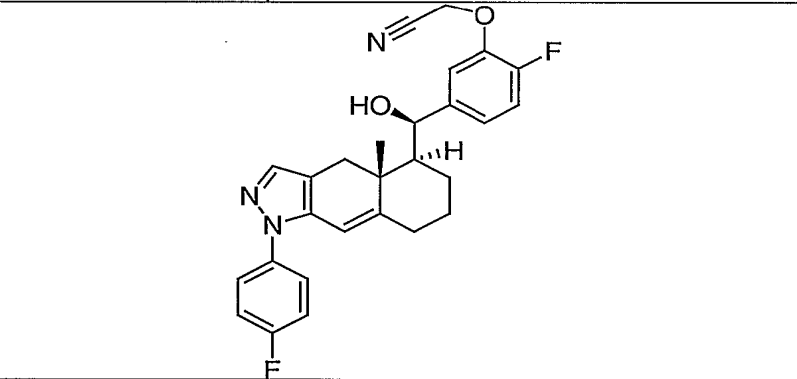
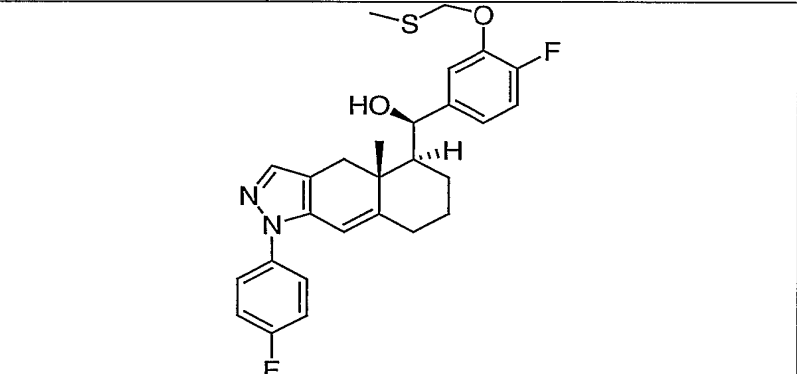
Example 73 (10.5 mg, 0.025 mmol) and Cs_2CO_3 (32.4 mg, 0.100 mmol) were combined in a 10 mL flask and DMF (1 mL) was added. Allyl iodide (5 μL , 0.055 mmol) was added and the reaction was stirred at room temperature for 1 hour. Next, the reaction was poured into H_2O (5 mL) and the aqueous solution was extracted with EtOAc (25 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (40% EtOAc/hexanes) afforded 11.4 mg (99%) of **Example 74**. R_f = 0.25 (40% EtOAc/hexanes). LCMS = 463; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.44-7.47 (m, 3H), 7.16 (t, J = 8.5 Hz, 2H), 7.05 (dd, J = 11.0, 8.0 Hz, 1H), 6.99 (dd, J = 8.5, 2.0 Hz, 1H), 6.85 (m, 1H), 6.11 (d, J = 1.5 Hz, 1H), 6.07 (m, 1H), 5.43 (dd, J = 17.5, 1.5 Hz, 1H), 5.31 (dd, J = 10.5, 1.0 Hz, 1H), 5.13 (s, 1H), 4.63 (d, J = 4.5 Hz, 1H), 3.17 (d, J = 15.0 Hz, 1H), 2.73 (d, J = 15.0 Hz, 1H), 2.40 (m, 1H), 2.28 (d, J = 15.0 Hz, 1H), 1.58-1.83 (m, 4H), 1.25 (s, 3H), 1.21 (m, 1H).

10

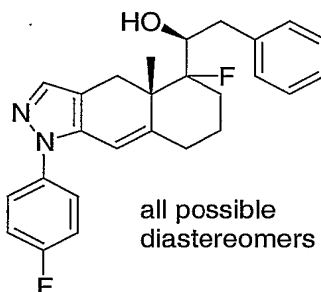
15

The following examples were synthesized following a procedure analogous to that described in Example 74:

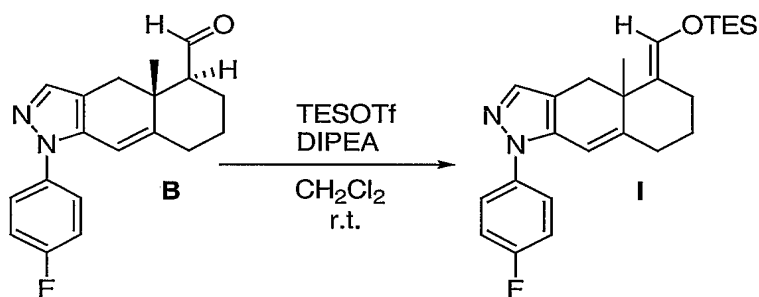
Compound	Molecular structure	LCMS (M+1) ⁺
75		451
76		465
77		481

78		513
79		477
80		462
81		483

EXAMPLE 82

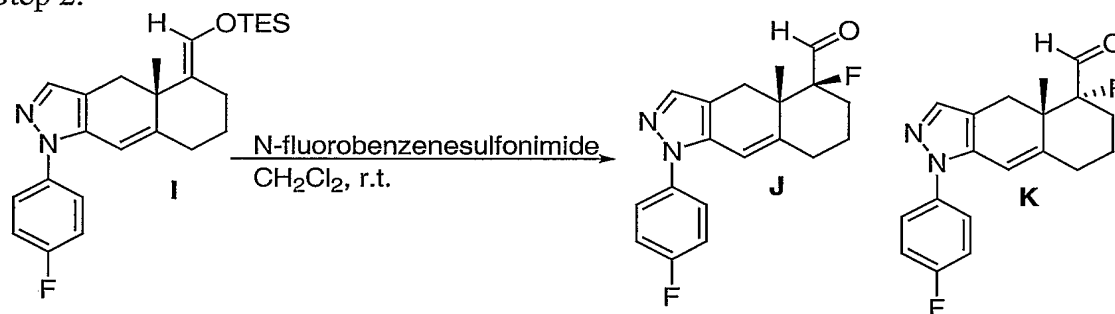


5 Step 1:



Aldehyde **B** (105.5 mg, 0.34 mmol) was dissolved in CH_2Cl_2 (8 mL) and *N,N*-diisopropylethylamine (1.42 mL, 8.16 mmol) was added followed by TESOTf (1.08 mL, 4.08 mmol). The reaction was stirred at room temperature for 6 h, quenched with 1 mL of isopropyl alcohol and diluted with EtOAc (50 mL). The organic solution was washed with saturated NaHCO_3 and brine (10 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (15% EtOAc/hexanes) to afford **I** which was used directly in the next reaction without further characterization.

Step 2:

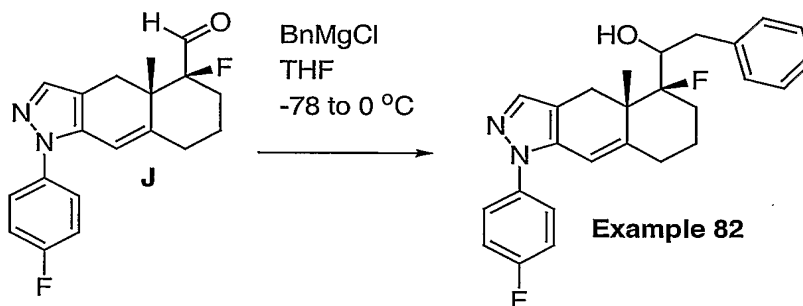


I was dissolved in CH_2Cl_2 (5 mL) and *N*-fluorobenzenesulfonimide (536 mg, 1.7 mmol) was added. The reaction was stirred at room temperature for 15 h and then concentrated. The residue was purified by flash chromatography (5 to 15% EtOAc/hexanes) to afford 52.1 mg (47%) of two separable diastereomers, 19.5 mg (18%) of the less polar diastereomer **J** and 32.6 mg (29%) of the more polar diastereomer **K**.

Less polar diastereomer **J**: $R_f = 0.24$ (50/42/8 hexanes/ CH_2Cl_2 /TBME). LCMS = 329; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 9.88 (d, $J = 7.1$ Hz, 1H), 7.42-7.45 (m, 2H), 7.37 (s, 1H), 7.14-7.18 (m, 2H), 6.25 (s, 1H), 2.89 (d, $J = 16$ Hz, 1H), 2.78 (d, $J = 16$ Hz, 1H), 2.53 (m, 1H), 2.33 (br d, $J = 14$ Hz, 1H), 2.06 (m, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.69 (m, 1H), 1.32 (d, $J = 1.4$ Hz, 3H).

More polar diastereomer **K**: $R_f = 0.21$ (50/42/8 hexanes/ CH_2Cl_2 /TBME). LCMS = 329; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 9.91 (d, $J = 5.7$ Hz, 1H), 7.42-7.45 (m, 3H), 7.16 (t, $J = 8.6$ Hz, 2H), 6.27 (d, $J = 2.1$ Hz, 1H), 3.51 (d, $J = 15.3$ Hz, 1H), 2.44-2.52 (m, 2H), 2.39 (br d, $J = 15.8$ Hz, 1H), 2.10 (m, 1H), 1.76-1.90 (m, 2H), 1.30 (m, 1H), 1.18 (s, 3H).

Step 3:



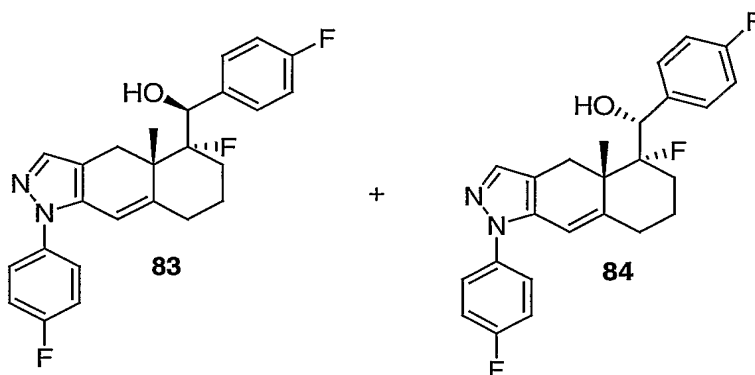
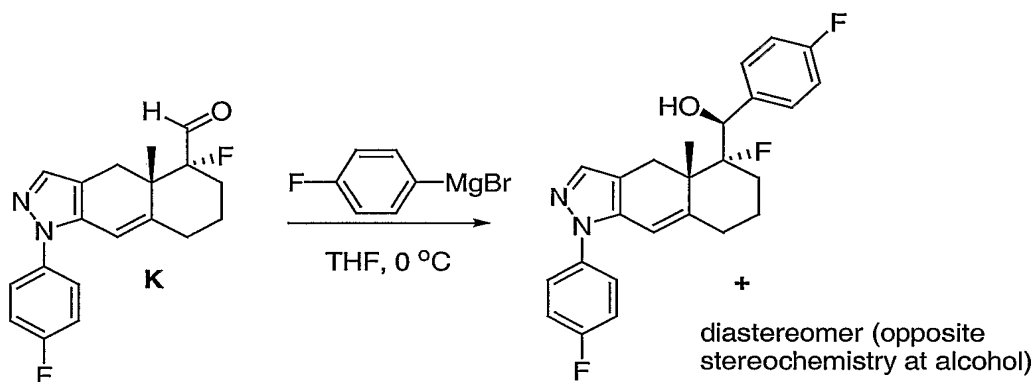
Fluoroaldehyde diastereomer **J** (17.6 mg, 0.054 mmol) was dissolved in THF (2mL) and cooled to -78°C . BnMgCl (536 μL of a 1 M solution in Et_2O , 0.536 mmol) was added dropwise by syringe. The reaction was warmed to 0°C for 10 min and then quenched with isopropyl alcohol (500 μL) and poured into saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (50mL). The organic layer was washed with H_2O and brine (15 mL each), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 15% EtOAc /hexanes) to give 5.3 mg (24%) of a less polar diastereomer of Example **82** and 3.8 mg (17%) of a more polar diastereomer of Example **82**.

Less polar diastereomer of Example **82**: $R_f = 0.40$ (25% EtOAc /hexanes, 2 elutions). LCMS = 421; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.41-7.44 (m, 2H), 7.38 (s, 1H), 7.31-7.34 (m, 2H), 7.24-7.26 (m, 3H), 7.12-7.16 (m, 2H), 6.14 (s, 1H), 4.21 (t, $J = 9.5$ Hz, 1H), 3.19 (d, $J = 16.0$ Hz, 1H), 3.11 (d, $J = 13.3$ Hz, 1H), 7.75 (dd, $J = 13.5, 10.5$ Hz, 1H), 2.67 (d, $J = 16.0$ Hz, 1H), 2.61 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 1.97-2.12 (m, 2H), 1.81 (m, 1H), 1.26 (d, $J = 2.5$ Hz, 3H).

More polar diastereomer of Example **82**: $R_f = 0.37$ (25% EtOAc /hexanes, 2 elutions). LCMS = 421; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.45 (dd, $J = 8.5, 4.8$ Hz, 2H), 7.42 (s, 3H), 7.33 (t, $J = 7.4$ Hz, 2H), 7.14-7.18 (m, 3H), 6.18 (s, 1H), 4.05 (dd, $J = 21, 10.5$ Hz, 1H), 3.12 (d, $J = 13.5$ Hz, 1H), 2.97 (s, 2H), 2.78 (dd, $J = 13.5, 10.4$ Hz, 1H), 2.69 (m, 1H), 2.24 (m, 1H), 1.89-2.05 (m, 3H), 1.79 (br s, 1H), 1.67 (m, 1H), 1.35 (d, $J = 3$ Hz, 1H).

The two other possible diastereomers of **82** were prepared in similar manner from the more polar fluoroaldehyde diastereomer **K**.

25

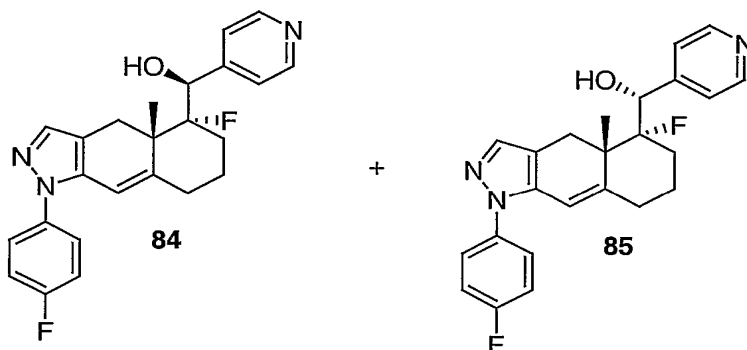
EXAMPLE 83 and 845 Step 1: Addition of Grignard Reagents to Fluoroaldehyde **K**Example **83** and **84**

Fluoroaldehyde **K** (28.7 mg, 0.0875 mmol) was dissolved in THF (6 mL) and
 10 cooled to 0 °C. 4-fluorobenzyl magnesium bromide (218 μ L of a 2.0 M solution in
 diethyl ether, 0.438 mmol) was added dropwise by syringe. The reaction was stirred
 at 0 °C for 1 hour and then quenched with saturated NH_4Cl (10 mL). The mixture
 was extracted with EtOAc (40 mL) and the organic layer was washed with H_2O and
 brine (10 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*.
 15 Purification by flash chromatography (5 to 80% EtOAc/hexanes) yielded a mixture of
 2 diastereomers. Further purification by PTLC (40/40/20 hexanes/ CH_2Cl_2 / Et_2O)
 afforded 18.4 mg (50%) of the less polar diastereomer and 11.1 mg (30%) of the more
 polar diastereomer.

Less Polar diastereomer: $R_f = 0.20$ (25% EtOAc/hexanes). LCMS = 425; $(M+1)^+$. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.43 (m, 2H), 7.40 (s, 1H), 7.36 (t, $J = 6$ Hz, 2H), 7.13 (t, $J = 8.4$ Hz, 2H), 7.05 (t, $J = 9$ Hz, 2H), 6.17 (s, 1H), 5.20 (s, 1H), 3.36 (d, $J = 15$ Hz, 1H), 2.81 (s, 1H), 2.77 (d, $J = 15$ Hz, 1H), 2.47 (m, 1H), 2.29 (m, 1H), 2.15 (m, 1H), 1.82 (m, 1H), 1.57 (m, 2H), 1.33 (s, 3H).

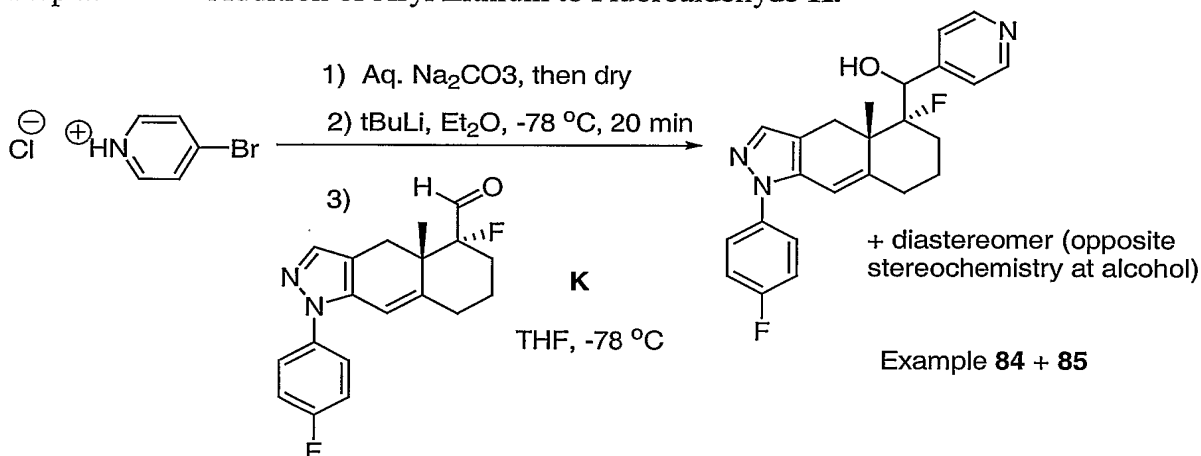
More Polar diastereomer: $R_f = 0.20$ (25% EtOAc/hexanes). LCMS = 425; $(M+1)^+$. $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.43-7.36 (m, 5H), 7.13 (t, $J = 8.4$ Hz, 2H), 7.05 (t, $J = 9$ Hz, 2H), 6.18 (s, 1H), 4.93 (d, $J = 15.5$ Hz, 1H), 3.42 (d, $J = 16$ Hz, 1H), 3.12 (d, $J = 16$ Hz, 1H), 2.52 (m, 1H), 2.36 (m, 1H), 1.90 (m, 1H), 1.66 (m, 1H), 1.03 (s, 3H).

EXAMPLE 84 and 85



15

Step 1: Addition of Aryl Lithium to Fluoroaldehyde **K**.

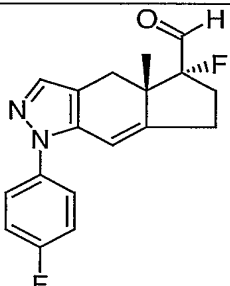


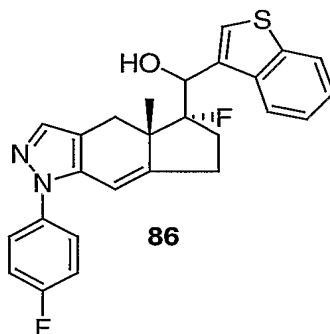
4-bromopyridine HCl (257.9 mg, 1.33 mmol) was dissolved in 5% Na₂CO₃ (8 mL). The solution was then extracted with Et₂O (12 mL) and the Et₂O layer was dried over Mg₂SO₄, filtered, and concentrated to dryness. The residue was azeotroped with benzene (1 mL) and was then dissolved in Et₂O (11.2 mL) and cooled to -78 °C. *t*-BuLi (527 µL of a 1.7 M solution in pentanes, 0.973 mmol) was added dropwise by syringe. The reaction was stirred at -78 °C for 20 minutes and then fluoroaldehyde **K** (29.0 mg, 0.088 mmol) in THF (3 mL) was added by cannula. The reaction was stirred at -78 °C for 45 minutes. 1 mL of isopropyl alcohol was added at -78 °C and then the reaction was poured into saturated NH₄Cl (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (20 to 100% EtOAc/hexanes) yielded a mixture of 2 diastereomers. Further purification using an AD chiral column (25% IPA/ heptanes) afforded 19.1 mg (53%) of peak 1 and 4.8 mg (13%) of peak 2.

Peak 1: *R_f* = 0.50 (100% EtOAc). LCMS = 408; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 8.42 (s, 2H), 7.40 (m, 2H), 7.36 (s, 1H), 7.34 (m, 2H), 7.12 (t, *J* = 8.4 Hz, 2H), 6.16 (s, 1H), 3.37 (d, *J* = 16 Hz, 1H), 2.77 (d, *J* = 16 Hz, 1H), 2.46 (m, 1H), 2.20 (m, 2H), 1.52 (m, 3H), 1.18 (s, 3H).

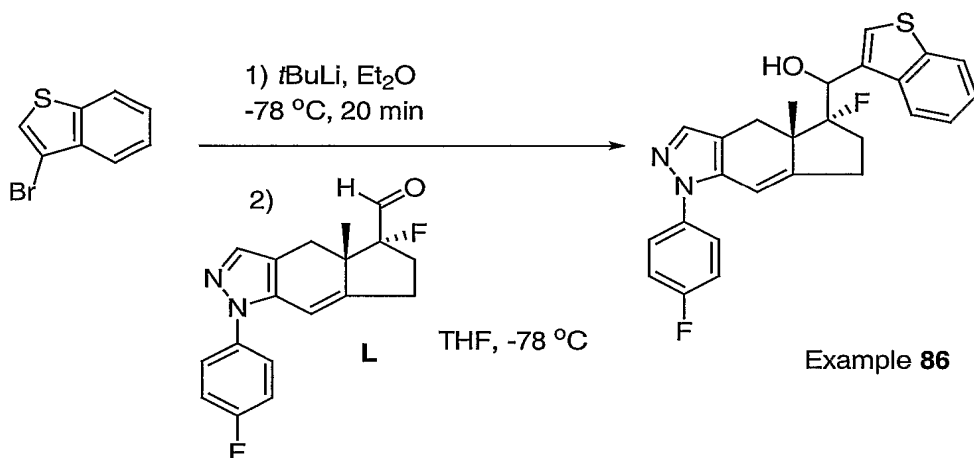
Peak 2: *R_f* = 0.50 (100% EtOAc). LCMS = 408; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 8.63 (s, 2H), 7.42 (m, 2H), 7.36 (m, 2H), 7.26 (s, 1H), 7.15 (t, *J* = 8.4 Hz, 2H), 6.29 (s, 1H), 4.92 (d, *J* = 18.6 Hz, 1H), 3.43 (d, *J* = 16 Hz, 1H), 3.13 (d, *J* = 15.6 Hz, 1H), 2.36 (m, 2H), 1.69 (m, 1H), 1.65 (m, 2H), 1.12 (s, 3H).

The following compound was synthesized following procedures analogous to those described for fluoroaldehyde **K** and beginning from aldehyde **F**:

Compound	Molecular structure	LCMS (M+1) ⁺
L		315

EXAMPLE 86

5

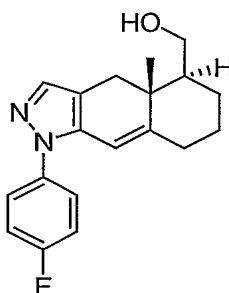
Step 1: Addition of Aryl Lithium to Fluoroaldehyde **L**.

10 A solution of 3-Bromothiophene (113.3 μ L, 0.866 mmol) in Et₂O (8 mL) was cooled to -78 °C and *t*-BuLi (1.01 mL of a 1.7 M solution in pentanes, 1.73 mmol) was added dropwise by syringe. The reaction was stirred at -78 °C for 20 minutes and then fluoroaldehyde **L** (27.2 mg, 0.0866 mmol) in THF (2 mL) was added by cannula. The reaction was stirred at -78 °C for 45 minutes. 1 mL of isopropyl alcohol was added at -78 °C and then the reaction was poured into saturated

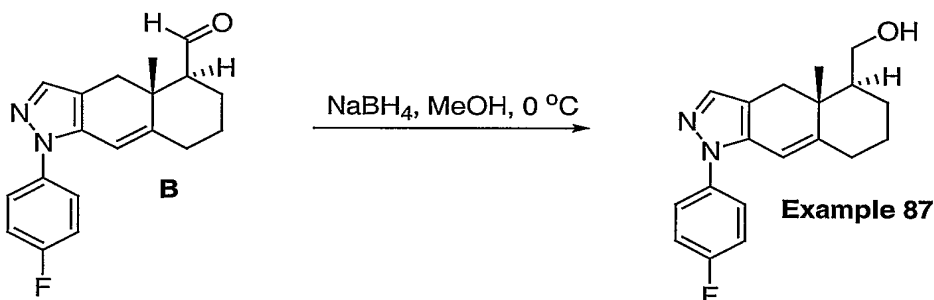
15 NH₄Cl (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 20% EtOAc/hexanes) followed by PTLC (20/40/40 hexanes/CH₂Cl₂/Et₂O) followed by an AD chiral column (25% IPA/heptanes)

afforded 1.6 mg (4%) of example **86**: $R_f = 0.43$ (60% EtOAc/hexanes). LCMS = 449; $(M+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.95 (d, $J = 7.8$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.65 (s, 1H), 7.42 (m, 4H), 7.15 (t, $J = 8.4$ Hz, 2H), 6.27 (s, 1H), 5.38 (dd, $J = 5.4$ Hz, 22.2 Hz, 1H), 3.38 (d, $J = 16.2$ Hz, 1H), 3.06 (d, $J = 16.2$ Hz, 1H), 2.58 (m, 2H), 2.04 (m, 1H), 1.73 (m, 1H), 1.36 (s, 3H).

EXAMPLE 87



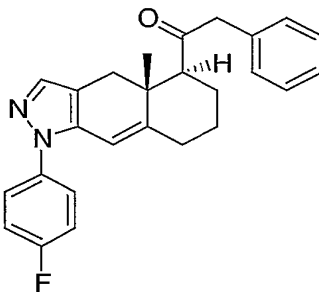
Step 1:



Aldehyde **B** (19.7 mg, 0.0635 mmol) was dissolved in MeOH (2 mL), and the solution was cooled to 0 °C. NaBH_4 (12 mg, 0.317 mmol) was added and the reaction was stirred at 0 °C for 30 min. 1 mL of saturated NH_4Cl was added to quench the reaction, and the mixture was extracted with EtOAc (25 mL). The organic layer was washed with H_2O and brine (10 mL each), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 30% EtOAc/hexanes) to afford 13.2 mg (67%) of **87** as a white solid (9:1 ratio of diastereomers). $R_f = 0.13$ (25% EtOAc/hexanes). LCMS = 313; $(M+1)^+$. ^1H NMR (major diastereomer) (CDCl_3 , 500 MHz) δ 7.43-7.47 (m, 2H), 7.40 (s, 1H), 7.15 (t, J

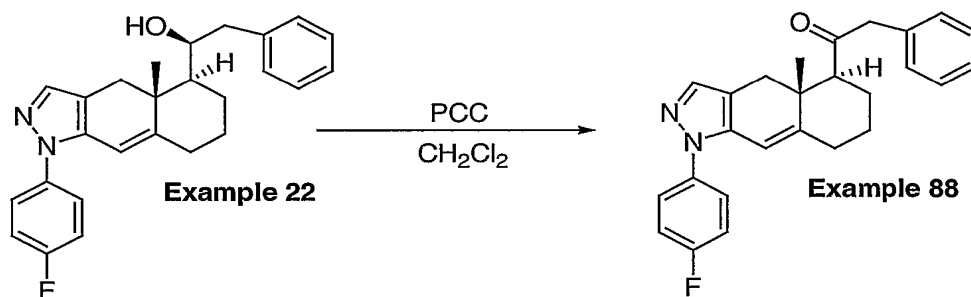
= 8.5 Hz, 1H), 6.12 (d, J = 1.9 Hz, 1H), 3.91 (dd, J = 10.5, 3.9 Hz, 1H), 3.51 (dd, J = 10.0, 8.9 Hz, 1H), 2.96 (d, J = 15.5 Hz, 1H), 2.66 (d, J = 15.5 Hz, 1H), 2.30-2.42 (m, 2H), 2.02 (m, 1H), 1.89 (m, 1H), 1.66 (m, 1H), 1.34-1.45 (m, 2H), 0.95 (s, 3H).

5

EXAMPLE 88

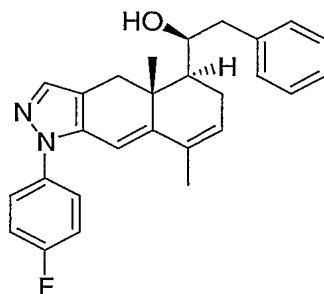
Step 1

10



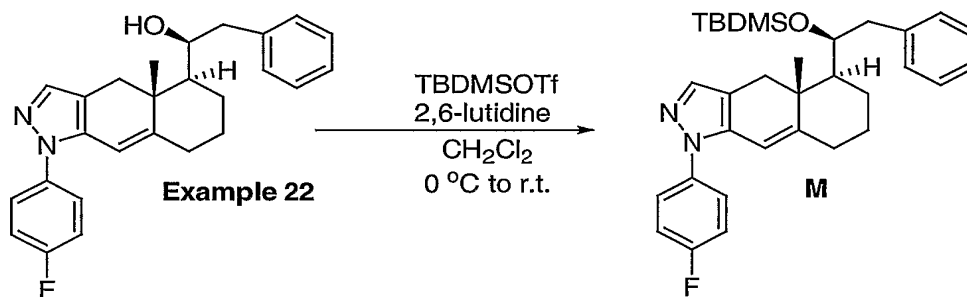
Example **22** (9.5 mg, 0.0236 mmol) was dissolved in CH_2Cl_2 (1 mL) and PCC (15.2 mg, 0.0708 mmol) was added. The reaction was stirred at room temperature for 1 hr and then diluted with hexanes (2 mL) and filtered through a plug of silica gel with 40% EtOAc/hexanes. The filtrate was concentrated and the residue was purified by preparatory thin layer chromatography (25% EtOAc/hexanes) to afford 5.0 mg (53%) of Example **88** as a white solid. R_f = 0.27 (25% EtOAc/hexanes). LCMS = 401; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.42-7.45 (m, 1H), 7.37 (s, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 7.3 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 7.13-7.22 (m, 1H), 6.11 (d, J = 2.3 Hz, 1H), 3.81 (d, J = 15.3 Hz, 1H), 3.77 (d, J = 15.3 Hz, 1H), 2.83 (dd, J = 12.5, 3.1 Hz, 1H), 2.76 (d, J = 15.2 Hz, 1H), 2.67 (d, J = 15.2 Hz, 1H), 2.42 (m, 1H), 2.29 (m, 1H), 1.77-1.89 (m, 2H), 1.67 (m, 1H), 1.35 (m, 1H), 1.20 (s, 3H).

EXAMPLE 89



5

Step 1:



10

Example **22** (165.9 mg, 0.412 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was cooled to 0 °C. 2,6-lutidine (265 μL , 2.27 mmol) and TBDMSOTf (142 μL , 0.618 mmol) were added and the reaction was allowed to warm to room temperature. After stirring for 16 h, additional 2,6-lutidine (300 μL , 2.58 mmol) and TBDMSOTf (300 μL , 1.31 mmol) were added to the reaction. The

15

reaction was stirred for an additional 3 h and then quenched with isopropyl alcohol (1 mL). The reaction was diluted with EtOAc (100 mL) and the organic solution was washed with saturated NaHCO_3 , brine, 1N HCl, saturated NaHCO_3 , and brine (25 mL of each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated.

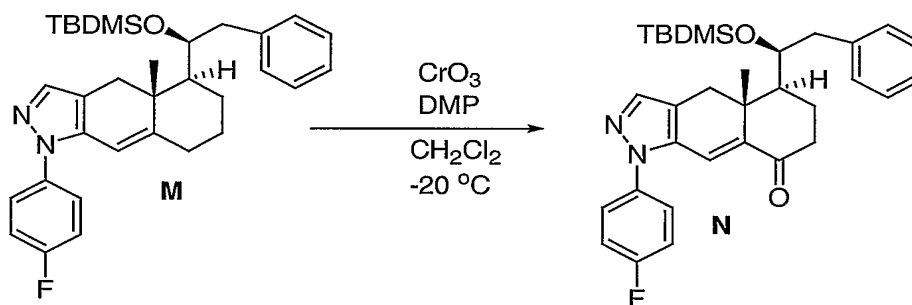
20

Purification by flash chromatography (15% TBME/hexanes) gave 207.1 mg (97%) of compound **M**. $R_f = 0.38$ (15% EtOAc/hexanes). ^1H NMR (CDCl_3 , 500 MHz) δ 7.37-7.39 (m, 2H), 7.26-7.30 (m, 3H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.10-7.14 (m, 4H), 5.98 (d, $J = 2.1$ Hz, 1H), 4.24 (dd, $J = 10.5, 4.0$ Hz, 1H), 2.96 (dd, $J = 13.0, 4.0$ Hz, 1H), 2.72 (dd, $J = 13.0, 10.5$ Hz, 1H), 2.55 (d, $J = 15.3$ Hz, 1H), 2.35 (m, 1H), 2.22

(bd, $J = 15.3$ Hz, 1H), 1.88 (m, 1H), 1.80 (m, 1H), 1.64-1.73 (m, 2H), 1.44 (dd, $J = 10.5, 3.0$ Hz, 1H), 1.28 (m, 1H), 1.02 (s, 3H), 0.94 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H).

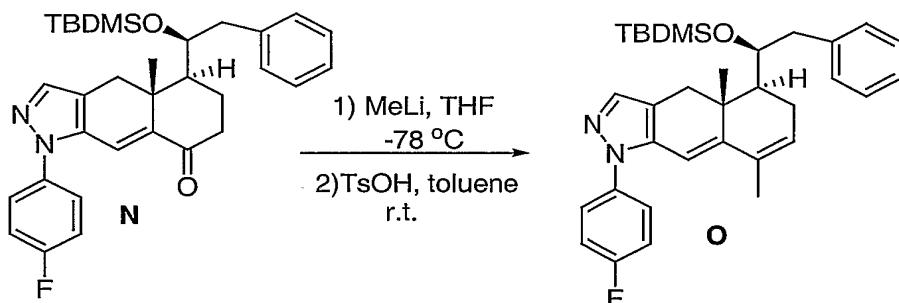
Step 2:

5



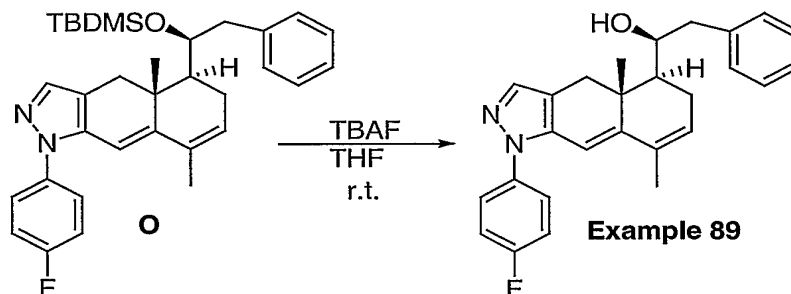
CrO_3 (550 mg, 5.5 mmol) was placed in a 50 mL roundbottom flask equipped with a stir bar, and 15 mL of dry CH_2Cl_2 was added. The suspension was cooled to $-20\text{ }^\circ\text{C}$ and 3,5-dimethylpyrrole (793 mg, 8.25 mmol) was added. The reaction was stirred for 15 min. at $-20\text{ }^\circ\text{C}$ and compound **M** (142 mg, 0.275 mmol) was added by cannula in CH_2Cl_2 (6mL). The reaction was stirred for 1.5 h while the temperature was maintained between -20 and $-15\text{ }^\circ\text{C}$. The reaction was then diluted with 100 mL of 3:1 hexanes/ Et_2O and filtered through a plug of silica gel. The filtrate was concentrated and the residue was purified by flash chromatography with 15% EtOAc /hexanes and then with 2% TBME/toluene to afford 20.8 mg (14%) of compound **N**. $R_f = 0.29$ (15% EtOAc /hexanes). LCMS = 531; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.44 (s, 1H), 7.39-7.41 (m, 2H), 7.29-7.32 (m, 2H), 7.22 (s, 1H), 7.13-7.21 (m, 5 H), 4.33 (dd, $J = 10.5, 4.0$ Hz, 1H), 3.04 (dd, $J = 13.0, 4.0$ Hz, 1H), 2.70-2.79 (m, 3H), 2.32 (m, 1H), 2.01-2.07 (m, 1H), 1.85 (d, $J = 16.1$ Hz, 1H), 1.75 (m, 1H), 1.11 (s, 3H), 0.93 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H).

Step 3:



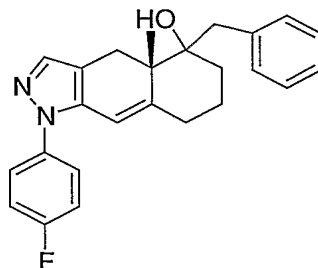
- 5 Compound **N** (15.8 mg, 0.0298 mmol) was dissolved in THF (4.5 mL) and the solution was cooled to -78°C and MeLi (42 μL of a 1.4 M solution in Et_2O (0.0596 mmol)) was added dropwise by syringe. The reaction was stirred for 15 min. at -78°C and then quenched with isopropyl alcohol (100 μL). The cold solution was poured into saturated NH_4Cl (10 mL) and the mixture was extracted with EtOAc (50
- 10 mL). The organic layer was washed with H_2O and brine (15 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude residue (17.0 mg) was dissolved in toluene (2 mL) and *p*-toluenesulphonic acid monohydrate (5 mg, 0.0263 mmol) was added. The reaction was stirred at room temperature for 15 min. and then diluted with EtOAc (40 mL). The organic solution was washed with saturated
- 15 NaHCO_3 and brine (15 mL of each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (15% EtOAc/hexanes) to afford 5.7 mg (36%) of compound **O**. $R_f = 0.30$ (15% EtOAc/hexanes). LCMS = 529; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.40-7.43 (m, 3H), 7.25-7.28 (m, 2H), 7.12-7.18 (m, 5H), 6.10 (s, 1H), 5.88 (d, $J = 5.5$ Hz, 1H), 4.40 (dd, $J = 10.3, 4.1$ Hz, 1H), 2.95 (dd, $J = 13.0, 4.1$ Hz, 1H), 2.70-2.75 (m, 2H), 2.61 (m, 1H), 2.25 (dt, $J = 19.0, 5.0$ Hz, 1H), 1.96 (d, $J = 15.4$ Hz, 1H),
- 20 1.76 (s, 3H), 1.73 (dd, $J = 12.5, 4.3$ Hz, 1H), 1.04 (s, 3H), 0.94 (s, 9H), 0.20 (s, 6H).

Step 4:

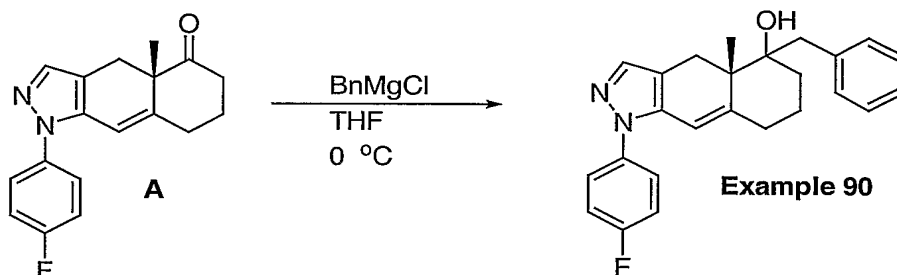


- 5 Compound **O** (5.7 mg, 0.0108 mmol) was dissolved in THF (3 mL) and TBAF (150 μ L of a 1 M solution in THF, 0.15 mmol) was added. The reaction was stirred at room temperature for 3 h and then poured into saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with H_2O and brine (15 mL each), dried over Na_2SO_4 , filtered, and
- 10 concentrated *in vacuo*. The residue was purified by preparatory thin layer chromatography (30% EtOAc/hexanes) to afford 3.5 mg (78%) of Example **89**. $R_f = 0.39$ (40% EtOAc/hexanes). LCMS = 415; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.46-7.48 (m, 2H), 7.43 (s, 1H), 7.41 (t, $J = 7.5$ Hz, 2H), 7.23-7.27 (m, 3H), 7.15-7.18 (m, 2H), 6.22 (s, 1H), 5.92 (d, $J = 5.5$ Hz, 1H), 4.31 (m, 1H), 2.97 (d, $J = 15.4$ Hz, 1H), 2.86 (dd, $J = 13.0, 9.0$ Hz, 1H), 2.70 (dd, $J = 13.0, 5.0$ Hz, 1H), 2.63 (m, 1H), 2.48 (d, $J = 15.1$ Hz, 1H), 2.31 (dt, $J = 18.7, 5.0$ Hz, 1H), 1.89 (dd, $J = 12.3, 4.3$ Hz, 1H), 1.83 (s, 3H), 1.14 (s, 3H).

EXAMPLE 90

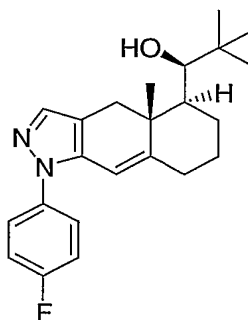


Step 1:

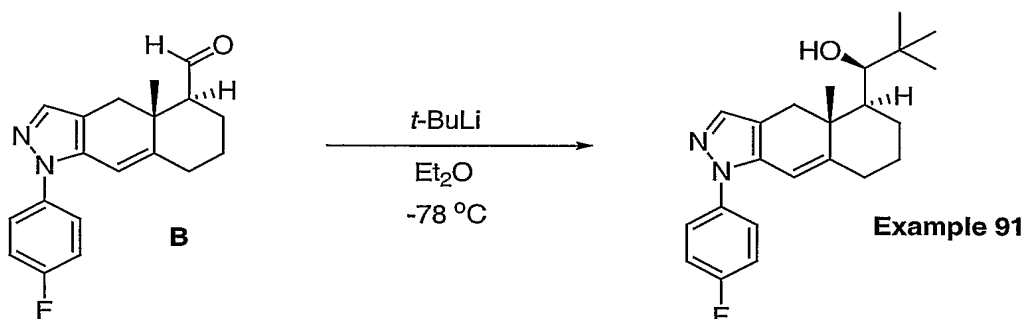


5 Ketone A (18.6 mg, 0.063 mmol) was dissolved in THF and cooled to 0 °C. BnMgCl (314 μ L of a 1 M solution in THF, 0.314 mmol) was added and the reaction was stirred at 0 °C for 1 hour. Saturated NH₄Cl (1 mL) was added to quench the reaction and the mixture was extracted with EtOAc (40 mL). The organic layer was washed with H₂O and brine (15 mL each), dried over Na₂SO₄, filtered, and
10 concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 20% EtOAc/hexanes) to afford 14.0 mg (57%) of Example **90**. R_f = 0.21 (25% EtOAc/hexanes). LCMS = 389; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.45-7.48 (m, 2H), 7.38 (s, 3H), 7.15-7.30 (m, 7H), 6.26 (s, 1H), 3.52 (d, *J* = 17.1 Hz, 1H), 2.98 (d, *J* = 14.0 Hz, 1H), 2.86 (d, *J* = 14.0 Hz, 1H), 2.68 (d, *J* = 17.1 Hz, 1H), 2.61 (m, 1H),
15 2.20 (dd, *J* = 9.0, 4.4 Hz, 1H), 1.61-1.75 (m, 3H), 1.46 (m, 1H), 1.37 (s, 3H).

EXAMPLE 91



Step 1:



5

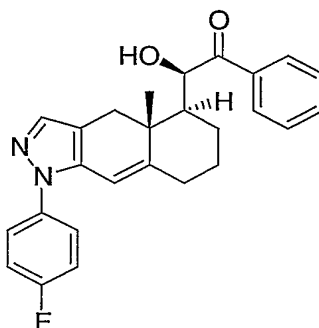
A solution of *t*-BuLi (150 μ L of a 1.7 M solution in pentanes, 0.258 mmol) in Et₂O (5 mL) was cooled to -78°C and aldehyde **B** (16.0 mg, 0.0516 mmol) was added as a solution in THF (2 mL). The reaction was allowed to warm slowly to -20°C and then cooled back to -78°C . The reaction was quenched by the addition of isopropyl alcohol (1 mL) and then poured into saturated NH₄Cl (10 mL). The mixture was extracted with EtOAc (40 mL), and the organic layer was washed with H₂O and brine (15 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 20% EtOAc/hexanes) to afford 8.0 mg (42%) of **91**. $R_f = 0.24$ (25% EtOAc/hexanes). LCMS = 369; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.43-7.46 (m, 2H), 7.41 (s, 1H), 7.14 (t, $J = 8.5$ Hz, 1H), 6.11 (d, $J = 1.6$ Hz, 1H), 3.49 (s, 1H), 2.83 (d, $J = 15.1$ Hz, 1H), 2.45 (d, $J = 15.1$ Hz, 1H), 2.39 (m, 1H), 2.32 (br d, $J = 14.6$ Hz, 1H), 1.59-1.86 (m, 3H), 1.41 (m, 1H), 1.07 (s, 3H), 0.96 (s, 9H).

10

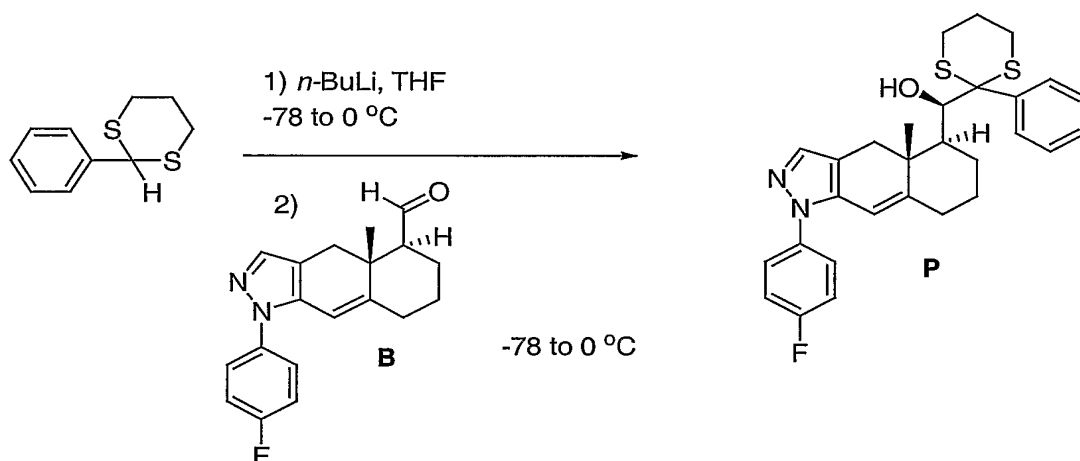
15

20

EXAMPLE 92



Step 1:



5

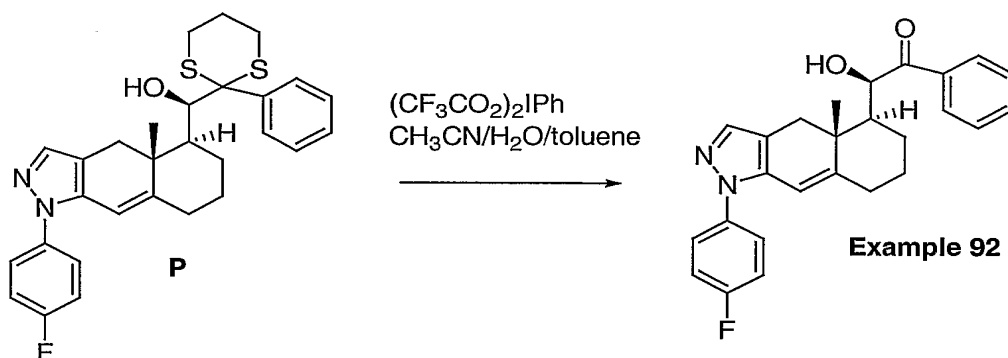
2-phenyl-1,3-dithiane (408 mg, 2.08 mmol) was dissolved in THF (8 mL) and cooled to -78 °C. *n*-BuLi (865 µL of a 1.6 M solution in hexanes, 1.38 mmol) was added and the reaction was warmed to 0 °C. The reaction was stirred at 0 °C for 30 min. and then cooled back to -78 °C. A solution of aldehyde **B** (53.7 mg, 0.173 mmol) was added in THF (2 mL) by cannula. The reaction was stirred at -78 °C for 10 min. and then warmed to 0 °C and stirred at that temperature for 1 hour. The reaction was quenched with isopropyl alcohol (1 mL) and then poured into saturated NH₄Cl (20 mL). The mixture was extracted with EtOAc (50 mL), and the organic layer layer was washed with H₂O and brine (20 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 15% EtOAc/hexanes) to afford 54.0 mg (62%) of **P**. *R_f* = 0.23 (25% EtOAc/hexanes). LCMS = 507; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.41-7.45 (m, 4H), 7.38 (s, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.13 (m, 2H), 6.04 (d, *J* = 2.1 Hz, 1H), 4.12 (m, 1H), 2.64-2.75 (m, 5H), 2.17-2.30 (m, 3H), 1.92-1.96 (m, 2H), 1.58 (m, 1H), 1.37 (qd, *J* = 13.5, 2.0 Hz, 1H), 1.18 (m, 1H), 1.00 (s, 3H), 0.90 (m, 1H).

10

15

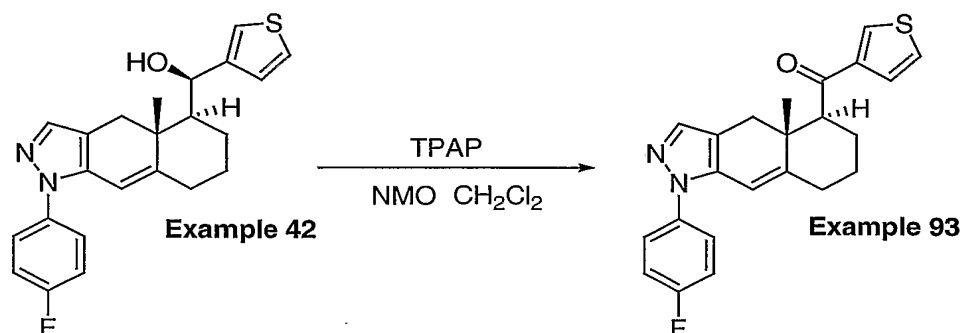
20

Step 2:

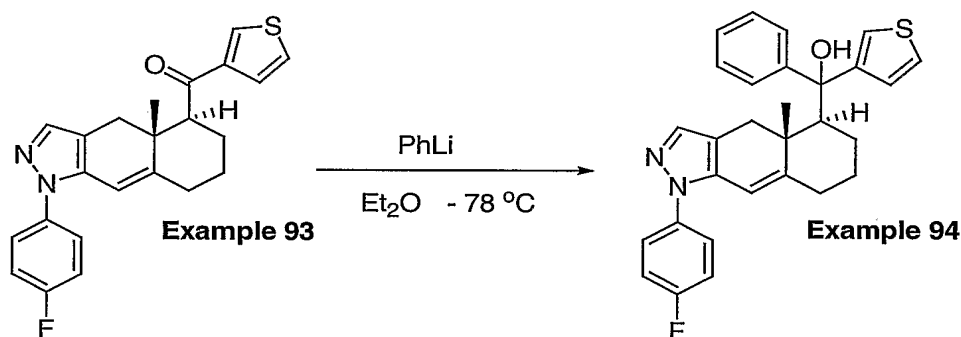


5 To dithiane **P** (10.3 mg, 0.020 mmol) was added CH_3CN (900 μL),
 toluene (200 μL), and H_2O (100 μL). The biphasic solution was stirred vigorously,
 and [bis(trifluoroacetoxy)iodo]benzene (17.5 mg, 0.041 mmol) was added. After 15
 min., an additional portion of [bis(trifluoroacetoxy)iodo]benzene (25 mg, 0.058 mmol)
 was added. The reaction was stirred for an additional 10 min. and then quenched with
 10 saturated NaHCO_3 (5 mL). The mixture was extracted with EtOAc (40 mL), and the
 organic layer was washed with brine (10 mL), dried over Na_2SO_4 , filtered and
 concentrated *in vacuo*. The residue was purified by preparatory thin layer
 chromatography to yield 4.4 mg (52%) of **92**. $R_f = 0.33$ (25% EtOAc/hexanes, 2
 elutions). LCMS = 417; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.90 (d, $J = 7.1$ Hz,
 2H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.49-7.63 (m, 3H), 7.42-7.45 (m, 2H), 7.13-7.17 (m,
 2H), 6.08 (d, $J = 2$ Hz, 1H), 5.44 (d, $J = 6.2$ Hz, 1H), 3.79 (d, $J = 6.2$ Hz, 1H), 3.30 (d,
 15 $J = 14.6$ Hz, 1H), 2.85 (d, $J = 14.7$ Hz, 1H), 2.36 (m, 1H), 2.22 (m, 1H), 1.90 (dd, $J =$
 12.5, 2.0 Hz, 1H), 1.76 (m, 1H), 1.70 (dd, $J = 12.5, 2.0$ Hz, 1H), 1.29 (s, 3H), 1.10-
 1.18 (m, 2H).

20



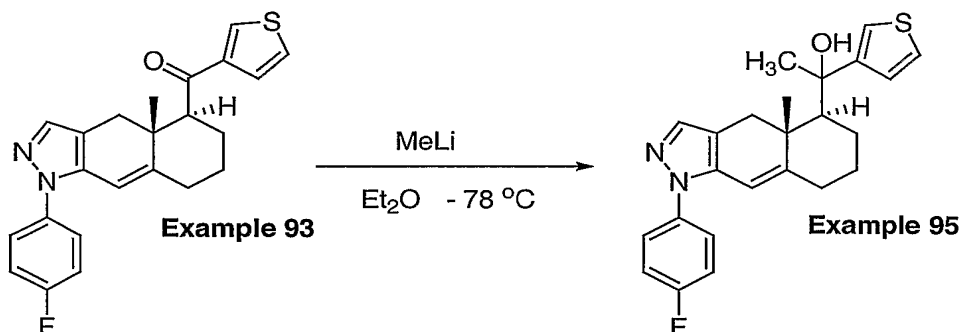
Example **42** (50 mg, 0.13 mmol) was dissolved in CH₂Cl₂ (8 mL) and NMO (22.8 mg, 0.195 mmol) was added. The reaction was stirred at 0 °C for 5 min. and TPAP (4.5 mg, 0.013 mmol) was added. Stirring was continued at 0 °C for an additional 1 h. The reaction was diluted with hexanes (2 mL) and filtered through a
 5 plug of silica gel with 10% EtOAc/hexanes to afford 40 mg (80%) of Example **93** as a yellow oil. R_f = 0.35 (25% EtOAc/hexanes). LCMS = 393; (M+1)⁺.



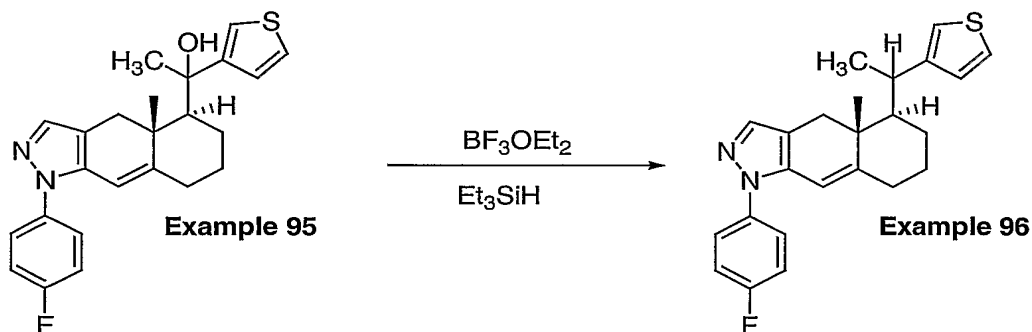
10

Example **93** (20 mg, 0.051 mmol) was dissolved in diethyl ether (5 mL) and the solution was cooled to -78 °C. Phenyl lithium (300 μL of a 1.8 M solution in Et₂O (0.53 mmol)) was added dropwise by syringe. The reaction was stirred for 1 h at -78 °C and then quenched with isopropyl alcohol (500 μL). The cold
 15 solution was poured into saturated NH₄Cl (10 mL) and the mixture was extracted with EtOAc (50 mL). The organic layer was washed with H₂O and brine (15 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by reverse-phase HPLC (20% AcCN/ H₂O) to afford 16 mg (67%) of Example **94** as a single diastereomer. R_f = 0.20 (30% EtOAc/hexanes). LCMS = 471; (M+1)⁺. ¹H
 20 NMR (CDCl₃, 500 MHz) δ 7.61-7.59 (m, 1H), 7.49-7.45 (m, 1H), 7.35-7.27 (m, 1H), 7.32-7.11 (m, 9H), 7.03-7.02 (dd, J = 3.5, 4.8 Hz, 1H), 6.13 (br s, 1H), 2.76 (dd, J = 3.4, 11.0 Hz, 1H), 2.58 (d, J = 16 Hz, 1H), 2.45-2.39 (m, 3H), 2.23 (d, J = 16.0 Hz, 1H), 1.04 (s, 3H).

25

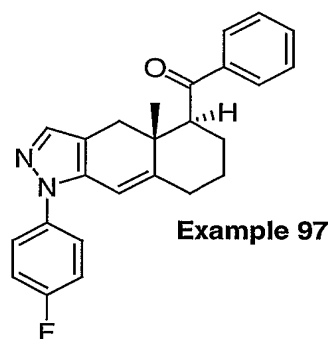


Example **93** (20 mg, 0.051 mmol) was dissolved in diethyl ether (5 mL) and the solution was cooled to -78°C . Methyl lithium (760 μL of a 1.4 M solution in Et_2O) was added dropwise by syringe. The reaction was stirred for 3 h at -78°C and then quenched with isopropyl alcohol (1 mL). The cold solution was poured into saturated NH_4Cl (10 mL) and the mixture was extracted with EtOAc (50 mL). The organic layer was washed with H_2O and brine (15 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (30% EtOAc /hexanes) to afford 8.8 mg (42%) of Example **95**. $R_f = 0.60$ (30% EtOAc /hexanes). LCMS = 409; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.48-7.45 (m, 2H), 7.31-7.27 (m, 2H), 7.29-7.14 (m, 1H), 6.13 (br s, 1H), 3.29 (d, $J = 16$ Hz, 1H), 2.70 (d, $J = 16$ Hz, 1H), 2.39-2.28 (m, 2H), 2.08-2.05 (m, 2H), 1.71 (s, 3H), 1.66-1.57 (m, 4H), 1.28 (s, 3H).



Example **95** (6.2 mg, 0.015 mmol) was dissolved in dichloromethane (7 mL) and the solution was cooled to 0°C . Boron trifluoride diethyl etherate (19 μL , 0.15 mmol) and triethylsilane (24 μL , 0.15 mmol) were added dropwise by syringe. The reaction was stirred for 1 h at 0°C and then quenched with saturated NaHCO_3 (2 mL). The solution was poured into H_2O (10 mL) and the mixture was

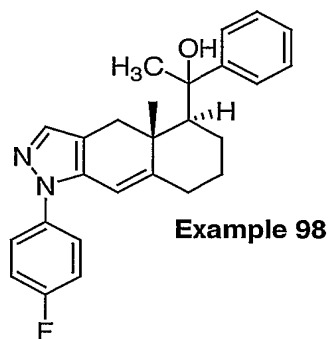
extracted with EtOAc (75 mL). The organic layer was washed with H₂O and brine (15 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 3.5 mg (59%) of Example **96**. R_f = 0.60 (15% EtOAc/hexanes). LCMS = 393; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.47-7.46 (m, 3H), 7.24 (dd, J = 4.9, 3.0 Hz, 1H), 7.17-7.14 (m, 3H), 6.13 (br s, 1H), 3.41-3.39 (dq, J = 7.3 Hz, 2.3 Hz, 1H), 3.11 (d, J = 15.4 Hz, 1H), 2.75 (d, J = 15.4 Hz, 1H), 2.32-2.23 (m, 2H), 1.89-1.84 (m, 2H), 1.71 (dt, J = 5.4, 2.8 Hz, 1H), 1.41-1.38 (m, 1H), (d, J = 7.3 Hz, 3H), 1.33-1.24 (m, 2H), 0.84 (s, 3H).



10

Example **35** and TPAP and NMO were processed as in Example **93** to provide the desired compound. R_f = 0.40 (25% EtOAc/hexanes). LCMS = 393; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.99-7.97 (m, 2H), 7.61-7.59 (m, 1H), 7.52 (t, J = 8.5 Hz, 1H), 7.47-7.43 (m, 4H), 7.19 (t, J = 8.5 Hz, 1H), 6.19 (br s, 1H), 3.73-3.70 (dd, J = 9.6 Hz, 2.7 Hz, 1H), 2.73 (d, J = 15.6 Hz, 1H), 2.51-2.40 (m, 2H), 2.38-2.35 (m, 1H), 2.07-1.99 (m, 2H), 1.81-1.77 (m, 1H), 1.27 (s, 3H).

15

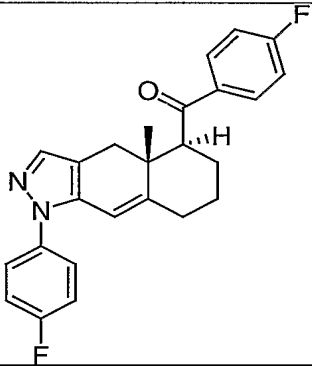
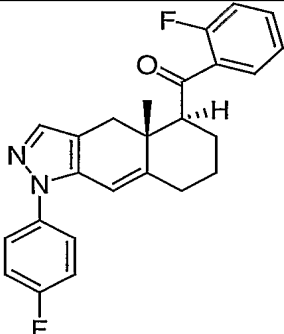


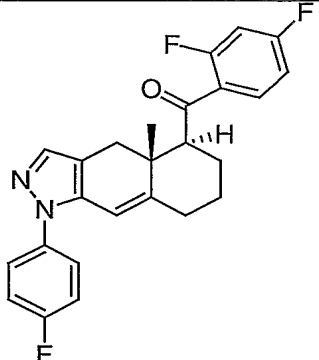
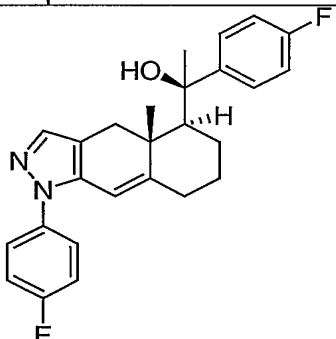
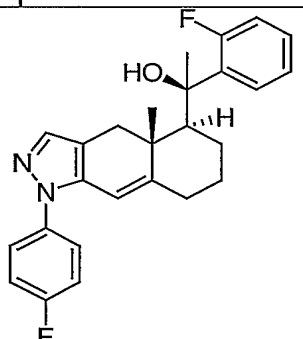
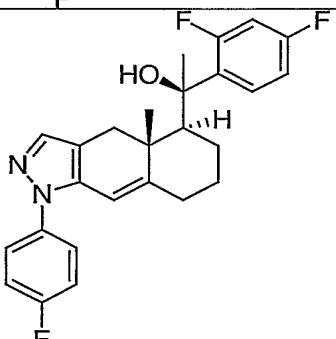
20

Example **97** and MeLi were processed as in Example **95** to provide the desired compound. $R_f = 0.30$ (25% EtOAc/hexanes). LCMS = 403; $(M+1)^+$. 1H NMR (CDCl₃, 500 MHz) δ 7.53-7.30 (m, 8H), 7.17-7.13 (m, 2H), 6.11 (br s, 1H), 3.16-3.13 (d, $J = 16$ Hz, 1H), 2.65-2.61 (d, $J = 16$ Hz, 1H), 2.47-2.30 (m, 2H), 1.70 (s, 3H),
 5 1.63-1.52 (m, 2H), 1.29 (s, 3H).

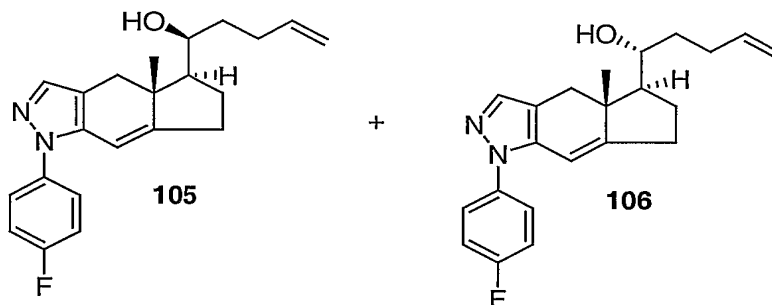
The following compounds were synthesized following procedures analogous to those described for examples 93 and 95:

10

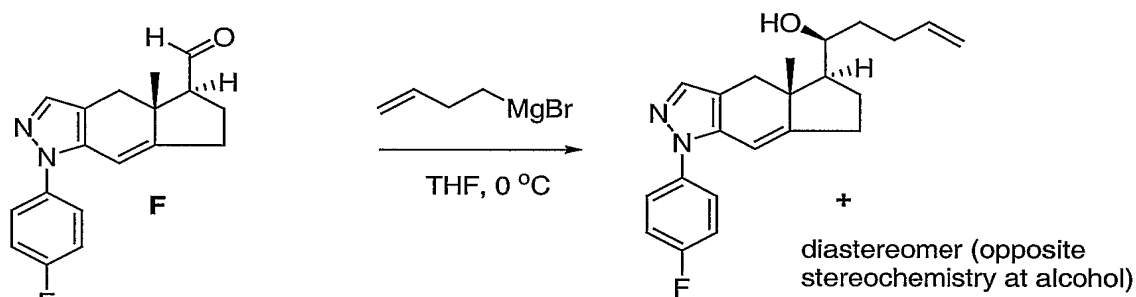
Compound	Molecular structure	LCMS $(M+1)^+$
99		405
100		405

101		423
102		421
103		421
104		439

EXAMPLE 105 and 106



5

Step 1: Addition of Grignard Reagents to Aldehyde **F**Example **105** and **106**

10

Aldehyde **F** (16.7 mg, 0.0564 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. 3-butenyl magnesium chloride (1.1 mL of a 0.5 M solution in THF, 0.564 mmol) was added dropwise by syringe. The reaction was stirred at 0 °C for 1 hour and then quenched with saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (40 mL) and the organic layer was washed with H_2O and brine (10 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The two diastereomeric products were isolated by flash chromatography (5 to 20% EtOAc/hexanes) to afford 9.6 mg (48%) of the less polar diastereomer and 5.0 mg (25%) of the more polar diastereomer. Less Polar diastereomer: $R_f = 0.17$ (25% EtOAc/hexanes). LCMS = 353; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.44-7.47 (m, 2H), 7.40 (s, 1H), 7.14 (t, $J = 8.5$ Hz, 2H), 6.13 (s, 1H), 5.88 (m, 1H), 5.10 (dd, $J = 17, 1.4$ Hz, 1H), 5.02 (d, $J = 10.3$ Hz, 1H), 3.77 (m, 1H), 2.85 (d, $J = 15.3$ Hz, 1H), 2.61 (m, 1H), 2.57 (d, $J = 15.3$ Hz, 1H), 2.42

15

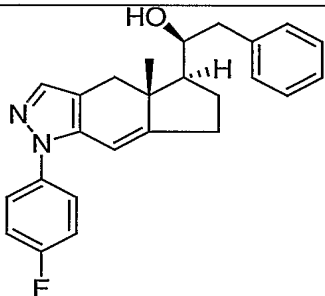
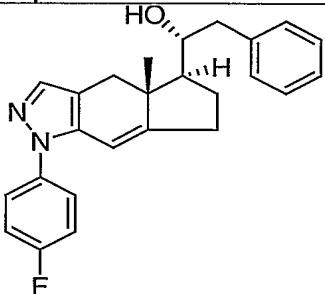
20

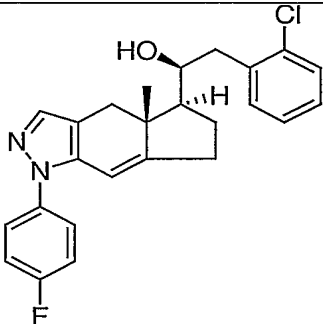
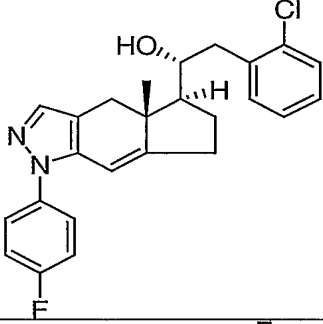
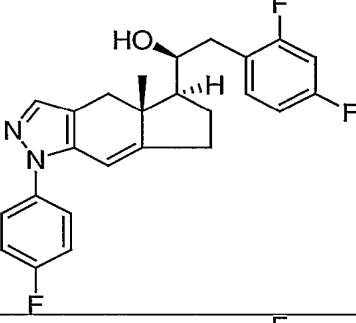
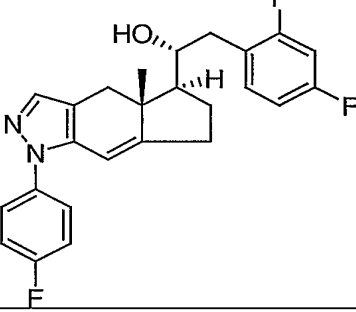
(m, 1H), 2.29 (m, 1H), 2.20 (m, 1H), 2.05 (m, 1H), 1.81-1.91 (m, 2H), 1.72 (m, 1H), 1.60 (m, 1H), 1.00 (s, 3H).

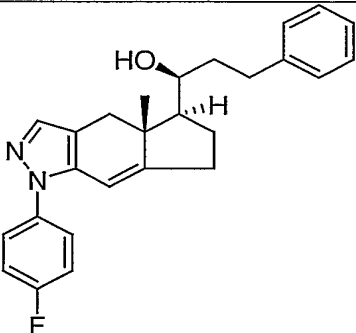
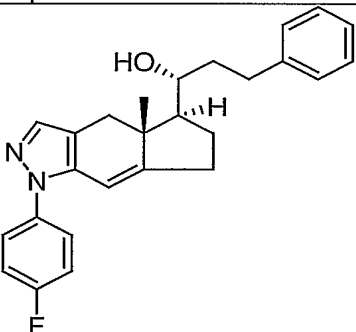
More Polar diastereomer: $R_f = 0.12$ (25% EtOAc/hexanes). LCMS = 353; $(M+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.45-7.48 (m, 2H), 7.39 (s, 1H), 7.14 (t, $J = 9.0$ Hz, 2H), 6.13 (s, 1H), 5.88 (m, 1H), 5.09 (dd, $J = 17, 1.4$ Hz, 1H), 5.01 (d, $J = 10.0$ Hz, 1H), 3.71 (m, 1H), 3.13 (d, $J = 15.3$ Hz, 1H), 2.65 (d, $J = 15.3$ Hz, 1H), 2.60 (m, 1H), 2.45 (m, 1H), 2.29 (m, 1H), 2.19 (m, 1H), 1.83-1.91 (m, 2H), 1.72 (m, 1H), 1.45-1.56 (m, 2H), 1.04 (s, 3H).

10

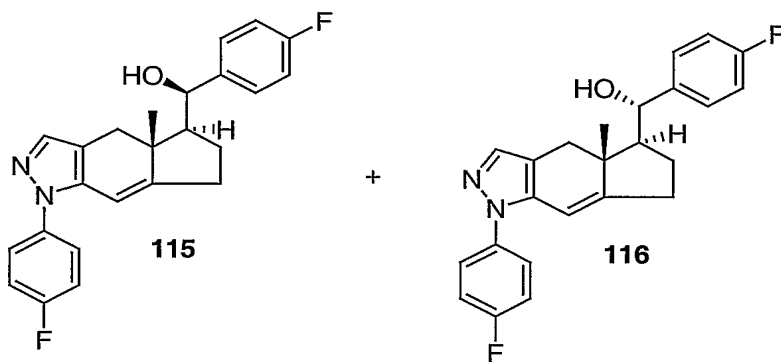
The following compounds were synthesized following procedures analogous to those described for examples **105** and **106**:

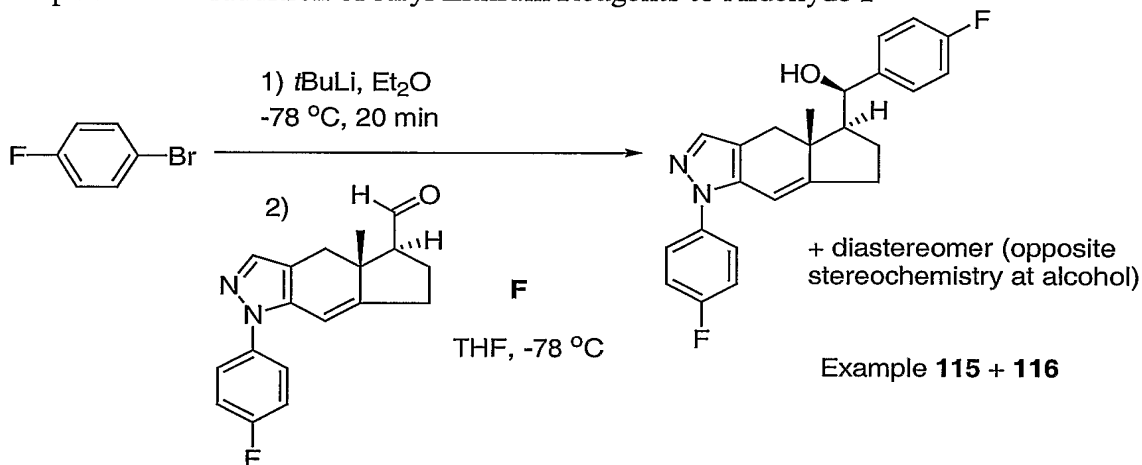
Compound	Molecular structure	LCMS $(M+1)^+$
107		389
108		389

109		423
110		423
111		425
112		425

113		403
114		403

EXAMPLE 115 and 116



Step 1: Addition of Aryl Lithium Reagents to Aldehyde **F**

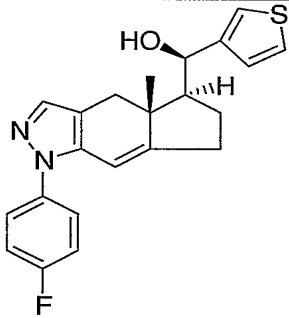
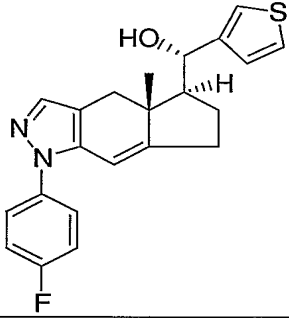
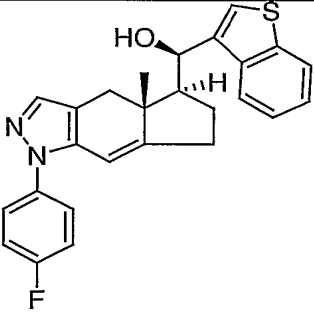
A solution of 1-Bromo-4-fluorobenzene (85 μ L, 0.777 mmol) in Et₂O (8 mL) was cooled to -78 °C and *t*BuLi (914 μ L of a 1.7 M solution in pentanes, 1.55 mmol) was added dropwise by syringe. The reaction was stirred at -78 °C for 20 minutes and then aldehyde **F** (23.0 mg, 0.0777 mmol) in THF (2 mL) was added by cannula. The reaction was stirred at -78 °C for 45 minutes. 1 mL of isopropyl alcohol was added at -78 °C and then the reaction was poured into saturated NH₄Cl (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 20% EtOAc/hexanes) yielded a mixture of 2 diastereomers. Further purification by PTLC (20/60/20 hexanes/CH₂Cl₂/Et₂O) afforded 13.8 mg (45%) of the less polar diastereomer and 9.0 mg (30%) of the more polar diastereomer.

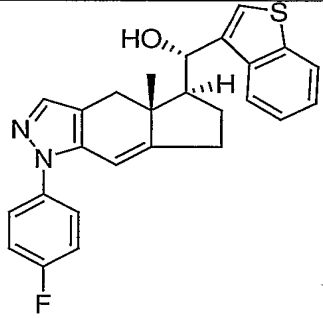
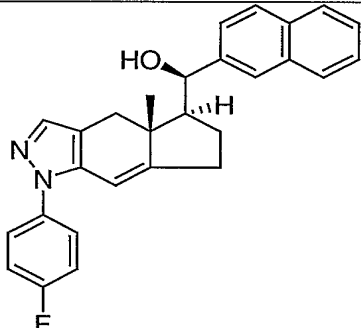
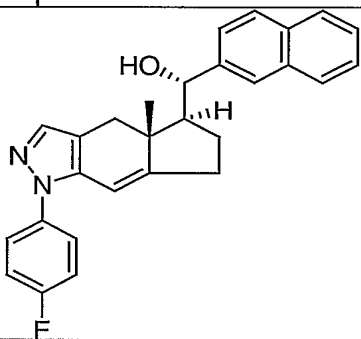
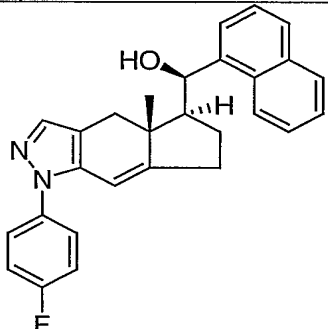
Less Polar diastereomer (**115**): R_f = 0.42 (20/60/20 hexanes/CH₂Cl₂/Et₂O). LCMS = 393; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.36-7.43 (m, 4H), 7.19 (s, 1H), 7.08-7.14 (m, 4H), 6.11 (s, 1H), 4.66 (d, *J* = 8.5 Hz, 1H), 2.63 (m, 1H), 2.45 (m, 1H), 2.22-2.32 (m, 2H), 2.09 (d, *J* = 15.6 Hz, 1H), 1.95 (m, 1H), 1.71 (d, *J* = 15.6 Hz, 1H), 1.00 (s, 3H).

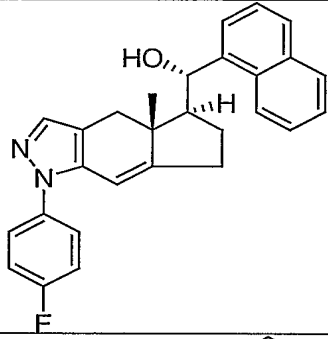
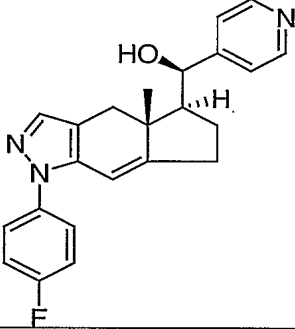
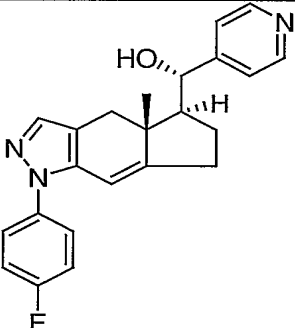
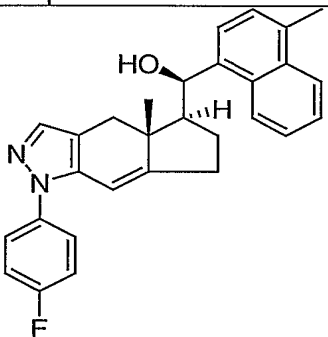
More Polar diastereomer (**116**): R_f = 0.20 (20/60/20 hexanes/CH₂Cl₂/Et₂O). LCMS = 393; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.45-7.48 (m, 2H), 7.41 (s, 1H), 7.33-7.36 (m, 2H), 7.12-7.15 (m, 2H), 7.03-7.06 (m, 2H), 6.14 (s, 1H), 4.64 (d, *J* = 10.1 Hz, 1H), 3.25 (d, *J* = 15.8 Hz, 1H), 2.78 (d, *J* = 15.8

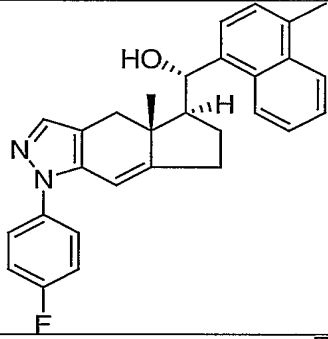
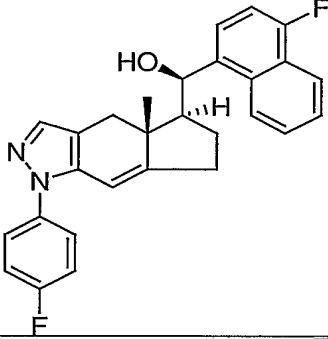
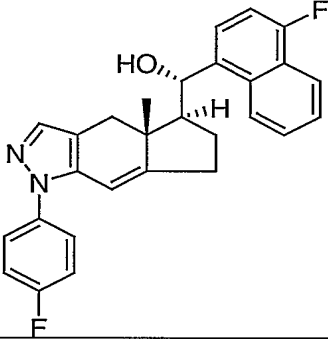
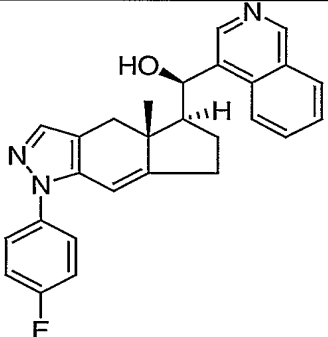
Hz, 1H), 2.53 (m, 1H), 2.33 (m, 1H), 2.17 (m, 1H), 1.93 (br s, 1H), 1.46 (m, 1H), 1.23 (m, 1H), 1.17 (s, 3H).

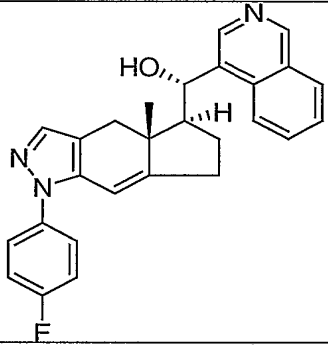
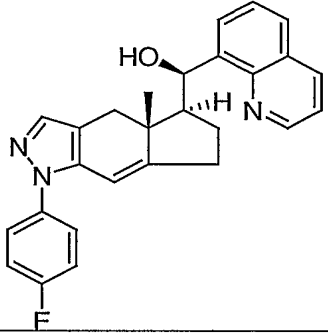
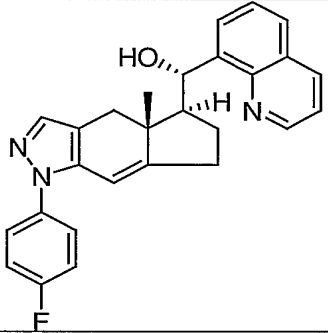
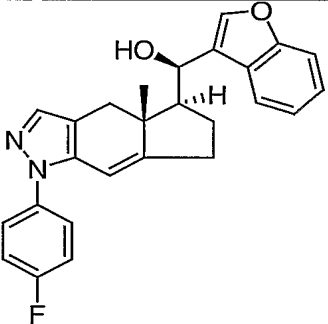
The following compounds were synthesized following procedures
5 analogous to that described for Examples **115** and **116**:

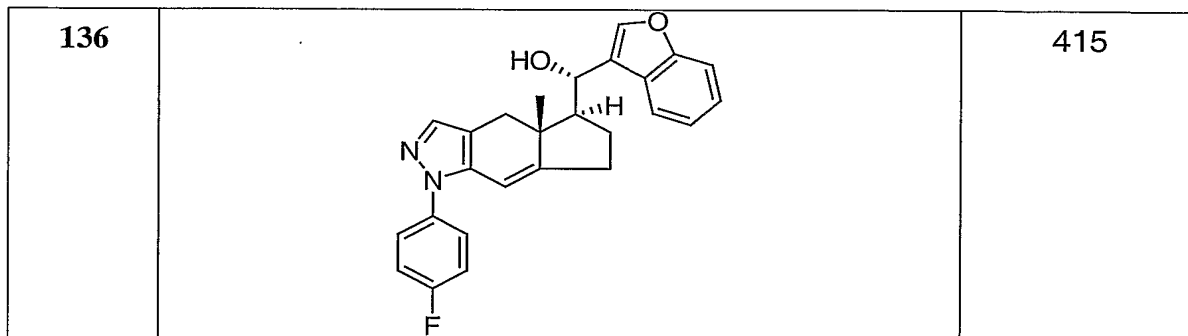
Compound	Molecular structure	LCMS (M+1) ⁺
117		381
118		381
119		431

120		431
121		425
122		425
123		425

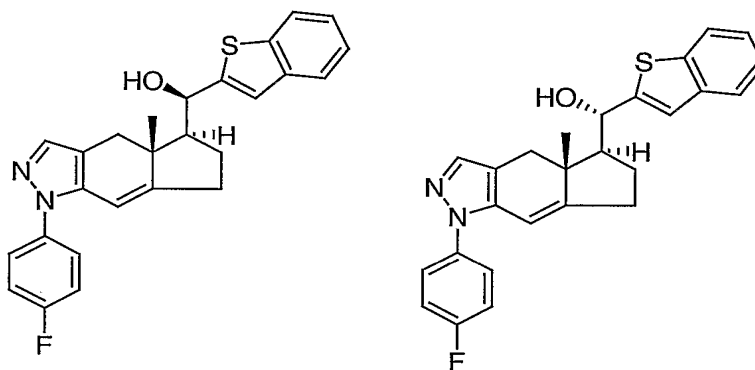
124		425
125		376
126		376
127		439

128		439
129		443
130		443
131		426

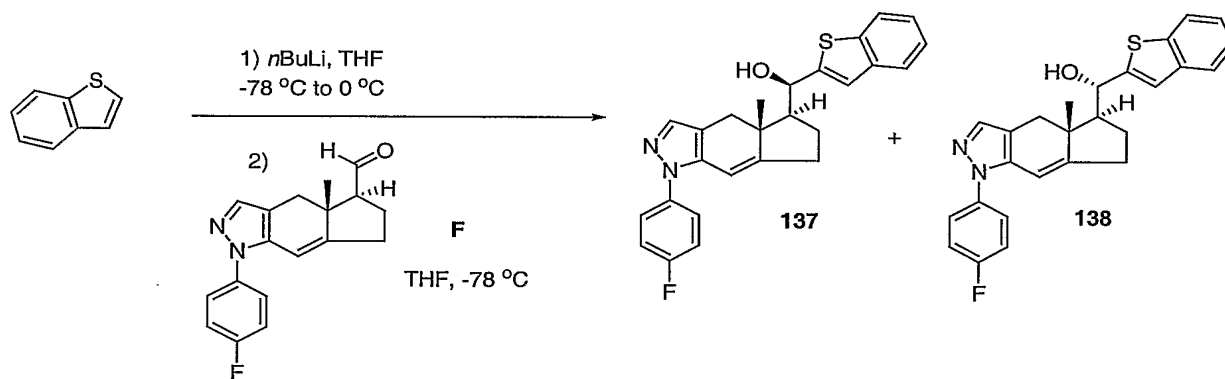
132		426
133		426
134		426
135		415

EXAMPLE 137+138

5



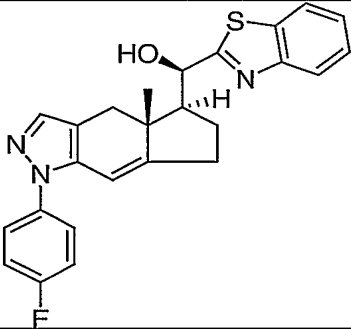
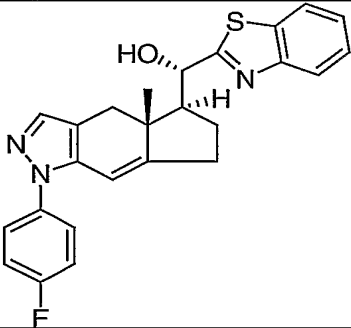
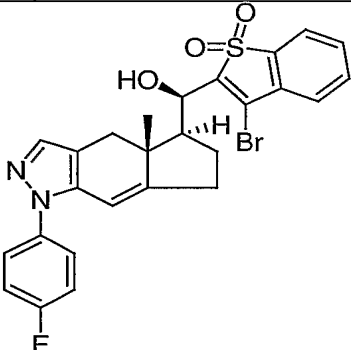
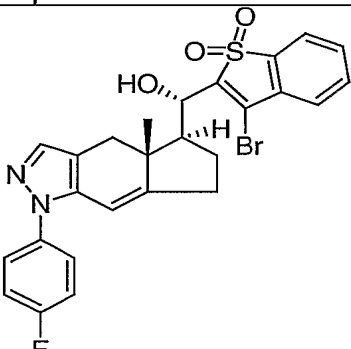
Step 1: Addition of Lithium Reagents generated by deprotonation with BuLi to Aldehyde **F**

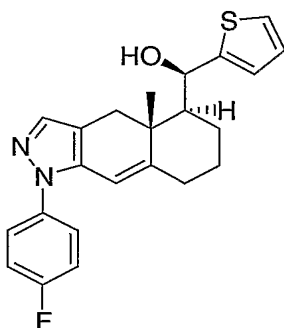


10

- A solution of benzothiophene (403 μ L, 3.45 mmol) in THF (16 mL) was cooled to -78°C and *n*BuLi (1.73 mL of a 1.6 M solution in hexanes, 2.76 mmol) was added dropwise by syringe. The reaction was warmed to 0°C for 15 minutes and then cooled back to -78°C . Aldehyde **F** (68.1 mg, 0.230 mmol) in THF (4 mL) was added by cannula and the reaction was stirred at -78°C for 45 minutes. 1 mL of isopropyl alcohol was added at -78°C and then the reaction was poured into saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (5 to 25% EtOAc/hexanes) gave the product as a mixture of diastereomers. The two diastereomers were separated by preparatory TLC in 40/40/20 CH_2Cl_2 /hexanes/ Et_2O followed by preparatory TLC in 50/50/3 hexanes/ CH_2Cl_2 /MeOH. 22.6 mg of **137** (23%) and 28.4 mg of **138** (29%) were isolated.
- Characterization for **137**: $R_f = 0.18$ (25% EtOAc/hexanes). LCMS = 431; $(\text{M} + 1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.87 (d, $J = 7.5$ Hz, 1H), 7.79 (d, $J = 7.0$ Hz, 1H), 7.35-7.44 (m, 4H), 7.30 (s, 1H), 7.17 (s, 1H), 7.12 (m, 2H), 6.14 (t, $J = 2$ Hz, 1H), 5.07 (dd, $J = 8.5, 3$ Hz, 1H), 2.66 (dd, $J = 19, 10.5$ Hz, 1H), 2.48 (m, 1H), 2.32-2.41 (m, 3H), 2.07-2.10 (m, 2H), 1.98 (m, 1H), 1.08 (s, 3H).
- Characterization for **138**: $R_f = 0.18$ (25% EtOAc/hexanes). LCMS = 431; $(\text{M} + 1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.84 (d, $J = 7.5$ Hz, 1H), 7.73 (d, $J = 7.0$ Hz, 1H), 7.47 (m, 2H), 7.42 (s, 1H), 7.33 (m, 2H), 7.23 (s, 1H), 7.14 (m, 2H), 6.16 (t, $J = 2.0$ Hz, 1H), 5.02 (dd, $J = 10.0, 3.0$ Hz, 1H), 3.25 (d, $J = 15.5$ Hz, 1H), 2.81 (d, $J = 15.5$ Hz, 1H), 2.58 (m, 1H), 2.34-2.44 (m, 2H), 2.11 (d, $J = 3$ Hz, 1H), 1.55 (m, 1H), 1.19 (s, 3H).

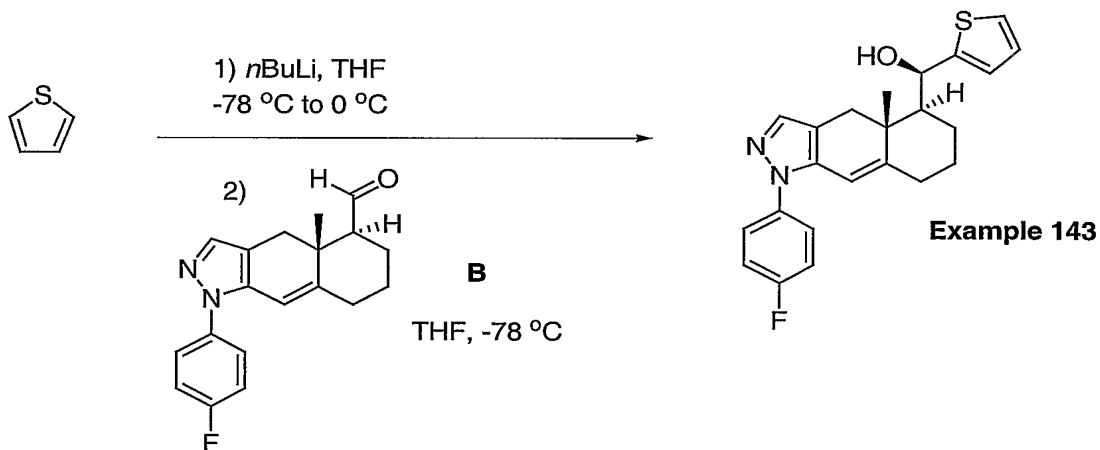
The following compounds were synthesized following procedures analogous to that described for examples **137** and **138**:

Compound	Molecular structure	LCMS (M+1) ⁺
139		432
140		432
141		543
142		543

EXAMPLE 143

5

Step 1: Addition of Lithium Reagents generated by deprotonation with BuLi to Aldehyde **B**



10

A solution of thiophene (82 μ L, 1.021 mmol) in THF (8 mL) was cooled to -78°C and *n*BuLi (510 μ L of a 1.6 M solution in hexanes, 0.816 mmol) was added dropwise by syringe. The reaction was warmed to 0°C for 15 minutes and then cooled back to -78°C . Aldehyde **B** (21.1 mg, 0.068 mmol) in THF (2 mL) was added by cannula and the reaction was stirred at -78°C for 45 minutes. 1 mL of isopropyl alcohol was added at -78°C and then the reaction was poured into saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (5 to 15%

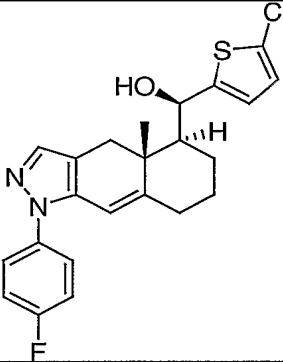
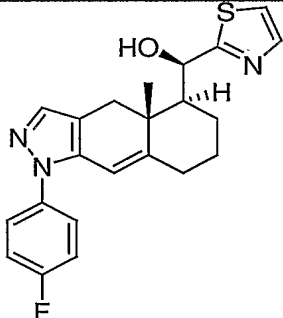
15

EtOAc/hexanes) afforded 20.5 mg (76%) of **143**. $R_f = 0.18$ (25% EtOAc/hexanes).
 LCMS = 395; $(M + 1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.44-7.46 (m, 2H), 7.43 (s, 1H), 7.22 (dd, $J = 5.0, 1.0$ Hz, 1H), 7.14-7.17 (m, 2H), 6.99 (dd, $J = 5.0, 3.5$ Hz, 1H), 6.95 (d, $J = 3.5$ Hz, 1H), 6.12 (d, $J = 2.2$ Hz, 1H), 5.38 (s, 1H), 3.10 (d, $J = 15.1$ Hz, 1H), 2.70 (d, $J = 15.1$ Hz, 1H), 2.42 (m, 1H), 2.31 (m, 1H), 2.2 (br s, 1H), 1.91 (dd, $J = 12.3, 3.4$ Hz, 1H), 1.88 (m, 1H), 1.70-1.79 (m, 2H), 1.33 (m, 1H), 1.23 (s, 3H).

The following compounds were synthesized following procedures analogous to that described in Example **143**:

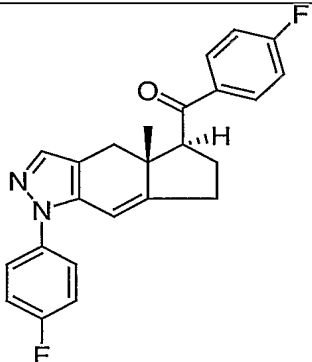
10

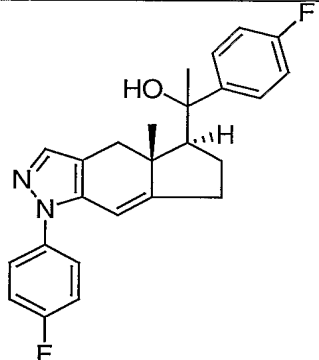
Compound	Molecular structure	LCMS $(M+1)^+$
144		445
145		413

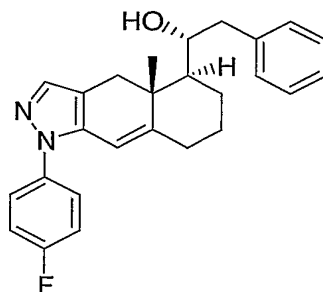
146		429
147		396

The following compounds were synthesized following procedures analogous to those described for examples **93** and **95** and starting from example **115/116**:

5

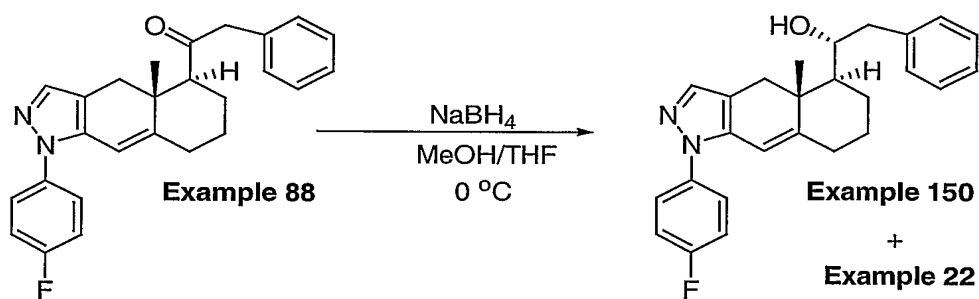
Compound	Molecular structure	LCMS (M+1) ⁺
148		391

149		407
-----	---	-----

EXAMPLE 150

5

Step 1. Reduction of Ketone



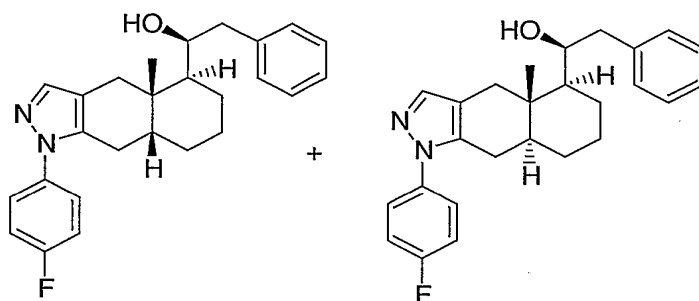
10

Example **88** (10.0 mg, 0.025 mmol) was dissolved in THF (1 mL) and MeOH (1 mL) was added. The solution was cooled to 0 °C and NaBH₄ (15 mg, 0.125 mmol) was added. The reaction was stirred at 0 °C for 2 hours and then quenched

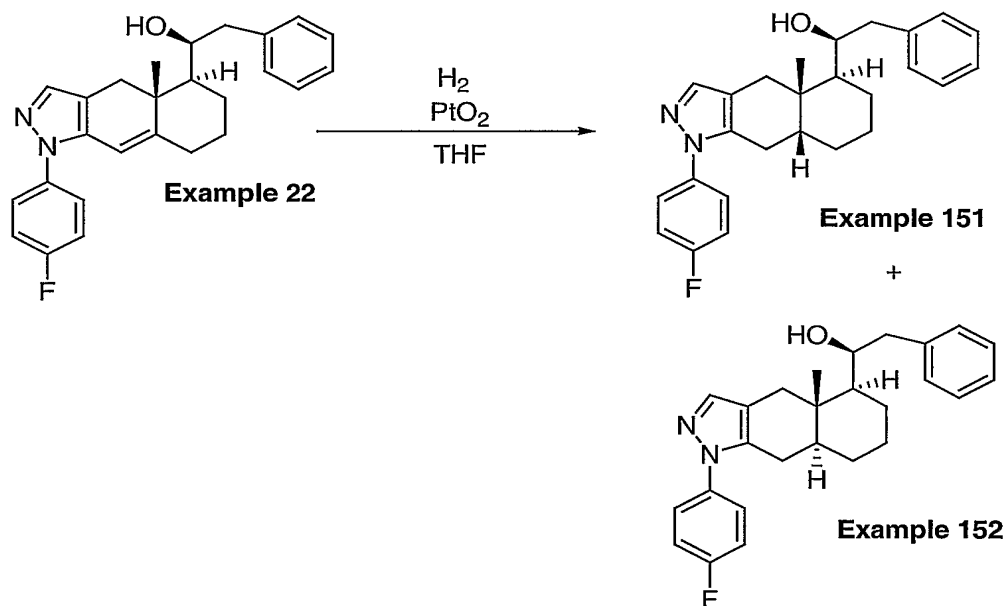
15 with saturated NH₄Cl (1 mL). The mixture was extracted with EtOAc (25 mL) and

the organic layer was washed with H₂O and brine (5 mL each). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by PTLC to afford 7.9 mg (79%) of alcohol as a 3:1 mixture of diastereomers favoring **150** over **22**. Further purification by chiral HPLC (OD column, 35% IPA/heptanes) gave 4.7 mg (47%) of pure **150** (slower eluting isomer). $R_f = 0.23$ (25% EtOAc/hexanes). LCMS = 403; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.45-7.47 (m, 2H), 7.40 (s, 1H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.28 (t, $J = 7.7$ Hz, 3H), 7.14-7.17 (m, 2H), 6.14 (s, 1H), 4.02 (m, 1H), 3.22 (d, $J = 15.5$ Hz, 1H), 3.03 (d, $J = 12.5$ Hz, 1H), 2.71 (d, $J = 15.5$ Hz, 1H), 2.60 (dd, $J = 13.1, 10.6$ Hz, 1H), 2.36 (m, 2H), 2.02 (m, 1H), 1.93 (m, 1H), 1.86 (dt, $J = 12.4, 3.6$ Hz, 1H), 1.39-1.55 (m, 2H), 1.14 (s, 3H).

EXAMPLE 151 and 152



Step 1.



5

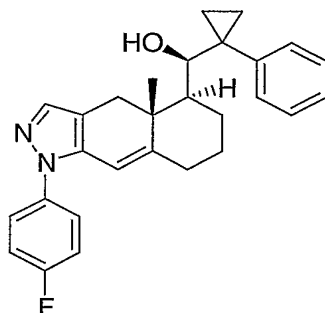
Example **22** (21.3 mg, 0.053 mmol) was dissolved in THF (3 mL) and PtO_2 (6 mg) was added. The solution was placed under H_2 and stirred at room temperature. After 3 hours, the catalyst was filtered off and the filtrate was concentrated. Purification by flash chromatography (5 to 20% EtOAc/hexanes) afforded 7.7 mg (36%) of **151** as a white solid and 9.2 mg (43%) of **152** as a white solid.

151 (Less Polar diastereomer): $R_f = 0.28$ (25% EtOAc/hexanes). LCMS = 405; $(M+1)^+$. 1H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.46 (m, 2H), 7.38 (s, 1H), 7.27 (t, $J = 7.4$ Hz, 2H), 7.19 (t, $J = 7.4$ Hz, 1H), 7.13 (m, 4H), 4.22 (m, 1H), 2.92 (d, $J = 16.0$ Hz, 1H), 2.81 (dd, $J = 13.3, 8.9$ Hz, 1H), 2.72 (dd, $J = 16.8, 6.2$ Hz, 1H), 2.62 (dd, $J = 13.3, 4.5$ Hz, 1H), 2.54 (dd, $J = 16.9, 6.1$ Hz, 1H), 2.15 (d, $J = 16.0$ Hz, 1H), 2.08 (br s, 1H), 1.86 (m, 1H), 1.79 (m, 1H), 1.67-1.72 (m, 2H), 1.59 (m, 1H), 1.28-1.37 (m, 2H), 1.15 (s, 3H).

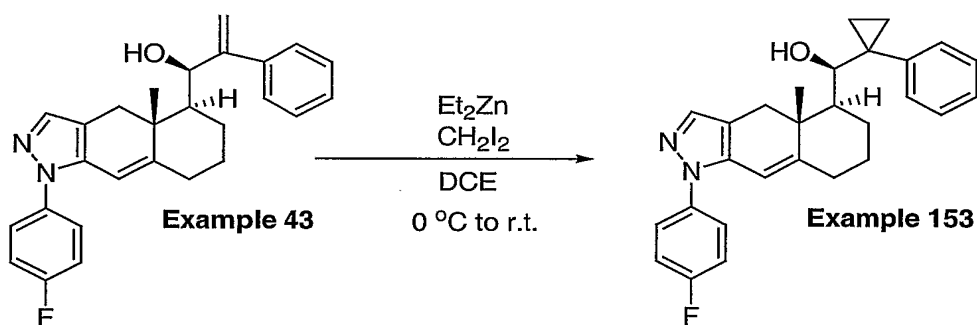
152 (More Polar diastereomer): $R_f = 0.21$ (25% EtOAc/hexanes). LCMS = 405; $(M+1)^+$. 1H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.48 (m, 2H), 7.42 (s, 1H), 7.35 (t, $J = 7.6$ Hz, 2H), 7.26 (t, $J = 7.9$ Hz, 3H), 7.12-7.15 (m, 2H), 4.26 (m, 1H), 2.90 (dd, $J = 13.3, 8.6$ Hz, 1H), 2.74 (d, $J = 15.4$ Hz, 1H), 2.72 (dd, $J = 13.3, 5.5$

Hz, 1H), 2.53 (dd, $J = 16.3, 4.8$ Hz, 1H), 2.38 (dd, $J = 16, 12$ Hz, 1H), 2.01 (d, $J = 15.1$ Hz, 1H), 1.91 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.57 (m, 1H), 1.51 (m, 1H), 1.34-1.43 (m, 2H), 1.29 (m, 1H), 0.95 (s, 3H).

5

EXAMPLE 153

10 Step 1. Cyclopropanation of the alkene

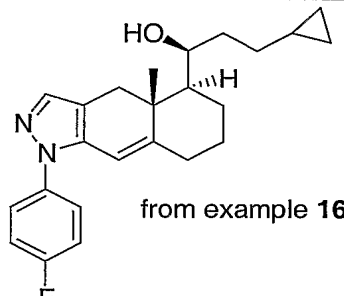


A solution of Et_2Zn (410 μL of a 1 M solution in hexanes, 0.41 mmol) in
 15 dichloroethane (1 mL) was cooled to 0 °C and CH_2I_2 (66 μL , 0.821 mmol) was added.
 The reaction was stirred for 5 minutes and the formation of a white precipitate was
 observed. A solution of **43** (17.0 mg, 0.041 mmol) in dichloroethane (1 mL) was
 added by cannula. The reaction was warmed to room temperature and stirred for 1
 hour. After this period of time, the reaction was quenched with 1 N HCl (1 mL). The
 20 mixture was extracted with EtOAc (50 mL). The organic layer was washed with H_2O ,
 aq. NaHSO_3 , saturated NaHCO_3 , and brine (15 mL each), dried over Na_2SO_4 , filtered,
 and concentrated *in vacuo*. Purification of the residue by flash chromatography (5 to
 20% EtOAc/hexanes) afforded 10.2 mg (58%) of **153**. $R_f = 0.14$ (25%)

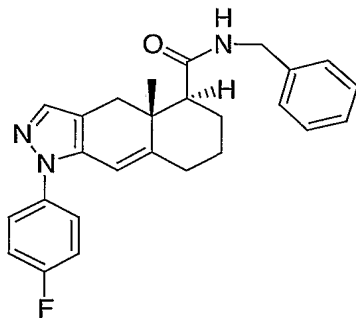
EtOAc/hexanes). LCMS = 429; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.37-7.44 (m, 5H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.12-7.16 (m, 2H), 6.05 (d, *J* = 2.1 Hz, 1H), 3.59 (s, 1H), 2.79 (d, *J* = 15.1 Hz, 1H), 2.19-2.31 (m, 3H), 1.83 (dd, *J* = 12.7, 3.0 Hz, 1H), 1.63 (m, 1H), 1.11-1.34 (m, 1H), 1.04 (s, 3H) 1.00 (m, 1H), 0.89 (m, 1H), 0.83 (m, 1H), 0.78 (m, 1H).

Example **154** was synthesized following procedures analogous to that described for Example **153**:

10

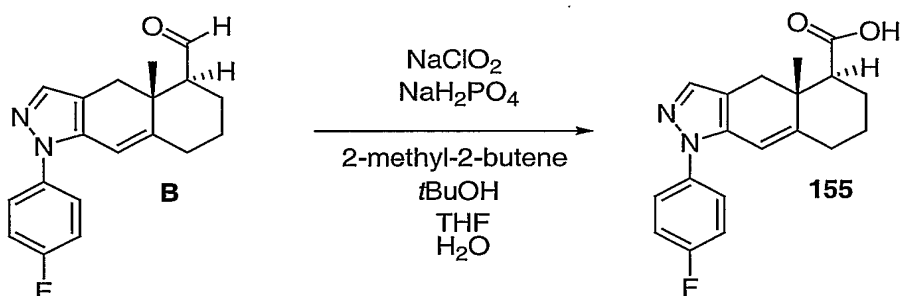
Compound	Molecular structure	LCMS (M+1) ⁺
154	 from example 16	381

EXAMPLE 156



15

Step 1.

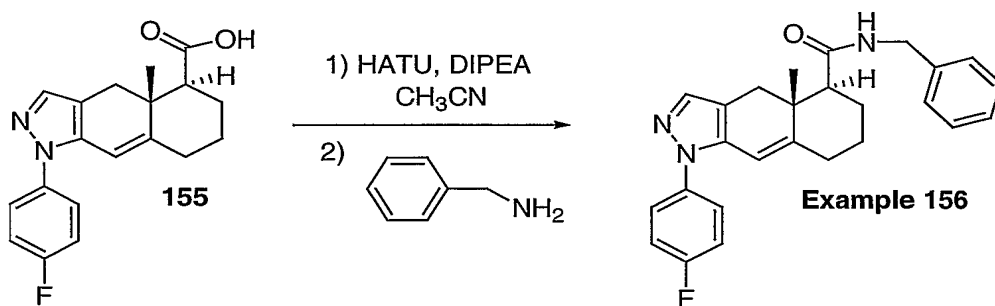


5

To a solution of aldehyde **B** (35.5 mg, 0.1145 mmol) in THF (200 μL) was added *t*BuOH (200 μL), 2-methyl-2-butene (200 μL), and a solution of NaClO_2 (23 mg, 0.252 mmol) and NaH_2PO_4 (35 mg, 0.252 mmol) in H_2O (250 μL). The reaction was stirred at room temperature for 2 hours and then partitioned between EtOAc and H_2O (25 mL of each). The aqueous layer was acidified with 1N HCl and extracted with EtOAc (3 x 25 mL). All of the organic extracts were combined and washed with brine (25 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (40/60/1 EtOAc/hexanes/HOAc) to afford 33.3 mg (89%) of acid **155**. $R_f = 0.22$ (40/60/1 EtOAc/hexanes/HOAc). LCMS = 327; $(\text{M} + 1)^+$.

15

Step 2. Coupling of carboxylic acid to amine



20

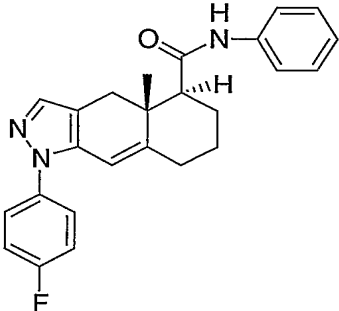
To a solution of **155** (10.5 mg, 0.0322 mmol) in CH_3CN (0.5 mL) was added DIPEA (23 μL , 0.129 mmol) and HATU (15 mg, 0.0387 mmol). The reaction was stirred at room temperature for 5 minutes and then benzylamine (6 μL , 0.0483 mmol) was added. After 30 minutes, the reaction was diluted with EtOAc (40 mL) and washed

with saturated NaHCO₃, brine, 1 N HCl, saturated NaHCO₃, and brine (10 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*.

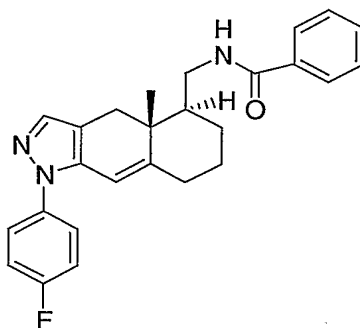
Purification by flash chromatography (20 to 60% EtOAc/hexanes) afforded 9.4 mg (70%) of **156**. R_f = 0.22 (40% EtOAc/hexanes). LCMS = 416; (M+1)⁺. ¹H NMR

- 5 (CDCl₃, 500 MHz) δ 7.41-7.44 (m, 2H), 7.29-7.38 (m, 6H), 7.12-7.16 (m, 2H), 6.11 (d, *J* = 1.8 Hz, 1H), 5.87 (t, *J* = 5.4 Hz, 1H), 4.47 (m, 2H), 2.81 (d, *J* = 15.3 Hz, 1H), 2.68 (d, *J* = 15.3 Hz, 1H), 2.43 (m, 1H), 2.29 (m, 1H), 2.25 (dd, *J* = 12.7, 3.3 Hz, 1H), 1.97 (qd, *J* = 13, 3.4 Hz, 1H) 1.89 (m, 1H), 1.79 (m, 1H), 1.37 (m, 1H), 1.19 (s, 3H).

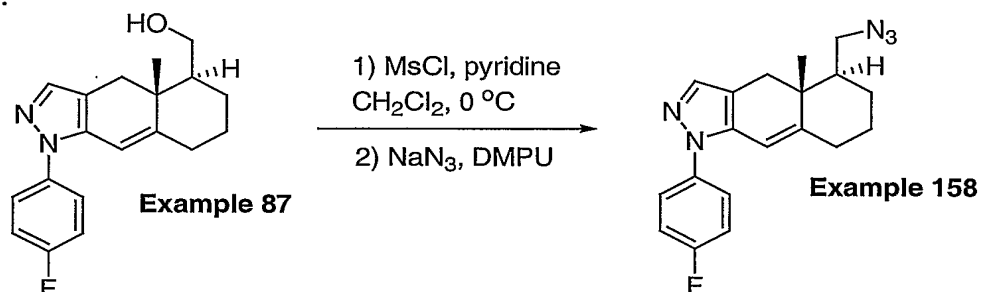
- 10 Example **157** was synthesized following procedures analogous to that described for Example **156**:

Compound	Molecular structure	LCMS (M+1) ⁺
157		402

15

EXAMPLE 159

Step 1.



5

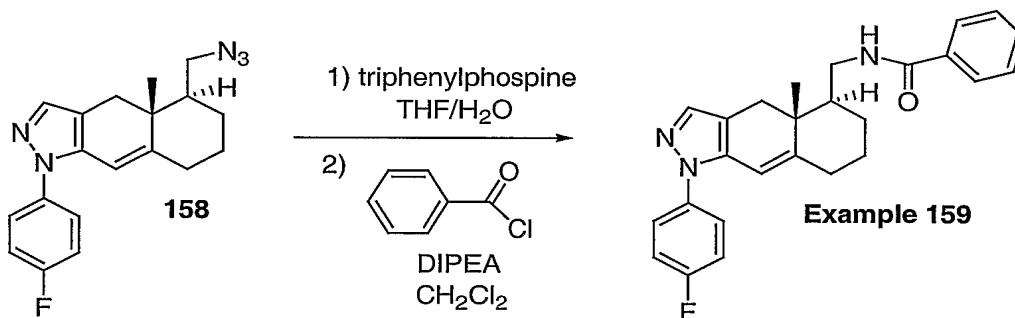
To a 0 °C solution of **87** (35.4 mg, 0.113 mmol) in CH₂Cl₂ was added pyridine (270 μL, 2.72 mmol) and MsCl (105 μL, 1.36 mmol). The reaction was stirred at 0 °C for 1 hour and then diluted with EtOAc (50 mL). The organic solution was washed with saturated NaHCO₃, H₂O, 1 N HCl, and brine (10 mL each). The organic layer was

10 dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was dissolved in DMPU (4 mL) and NaN₃ (37 mg, 0.565 mmol) was added. The reaction was stirred at room temperature for 3 days and then heated to 50 °C for 6 hours. The reaction was cooled to room temperature, diluted with EtOAc (50 mL), and washed with H₂O and brine (10 mL each). The organic layer was dried over Na₂SO₄, filtered,

15 and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexanes) afforded 32.2 mg (84%) of **158**. *R_f* = 0.38 (25% EtOAc/hexanes). LCMS = 338; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.43-7.46 (m, 2H), 7.41 (s, 1H), 7.13-7.17 (m, 2H), 6.14 (d, *J* = 1.9 Hz, 1H), 3.61 (dd, *J* = 12.1, 3.7 Hz, 1H), 3.11 (dd, *J* = 12.0, 9.7 Hz, 1H), 2.91 (d, *J* = 15.4 Hz, 1H), 2.63 (d, *J* = 15.4 Hz, 1H), 2.29-

20 2.40 (m, 2H), 1.97 (m, 1H), 1.87 (m, 1H), 1.71 (m, 1H), 1.31-1.43 (m, 2H), 0.96 (s, 3H).

Step 2.



5

To a solution of **158** (3.8 mg, 0.0113 mmol) in THF (300 μ L) was added triphenylphosphine (10 mg, 0.0381 mmol) and water (20 μ L). The reaction was stirred at room temperature overnight, and then DIPEA was added (50 μ L). The reaction was diluted with CH₂Cl₂ (30 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (1 mL) and DIPEA (100 μ L, 0.574 mmol) and benzoyl chloride (20 μ L, 0.172 mmol) were added. The reaction was stirred at room temperature for 10 minutes, diluted with EtOAc (25 mL) and washed with saturated NaHCO₃, brine, 1 N HCl, and brine (5 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (60% EtOAc/hexanes) afforded 4.1 mg (88%) of **159**. R_f = 0.35 (60% EtOAc/hexanes). LCMS = 416; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.78 (d, J = 7.4 Hz, 2H), 7.43-7.52 (m, 6H), 7.15 (t, J = 8.5 Hz, 2H), 6.20 (s, 1H), 6.13 (d, J = 1.6 Hz, 1H), 3.75 (m, 1H), 3.32 (m, 1H), 3.07 (d, J = 15.3 Hz, 1H), 2.78 (d, J = 15.3 Hz, 1H), 2.40 (m, 1H), 2.32 (m, 1H), 1.88 (m, 2H), 1.76 (m, 1H), 1.32-1.50 (m, 2H), 1.05 (s, 3H).

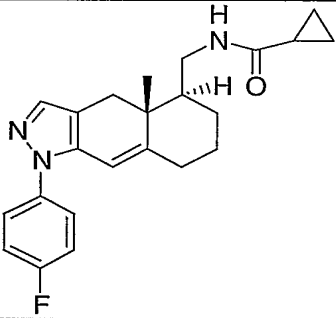
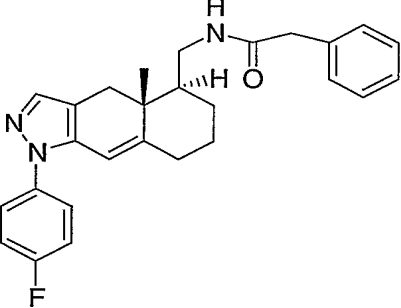
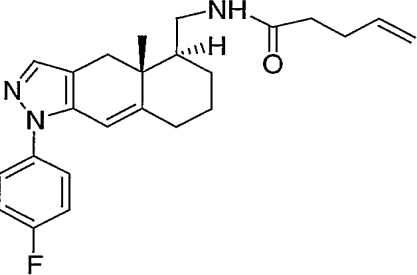
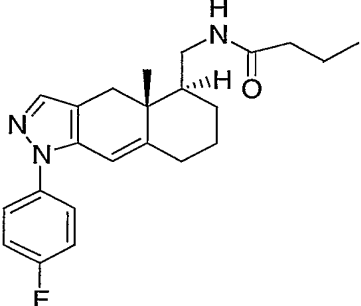
10

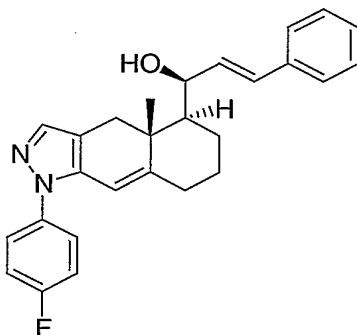
15

20

The following compounds were synthesized following procedures analogous to that described for Example **159**:

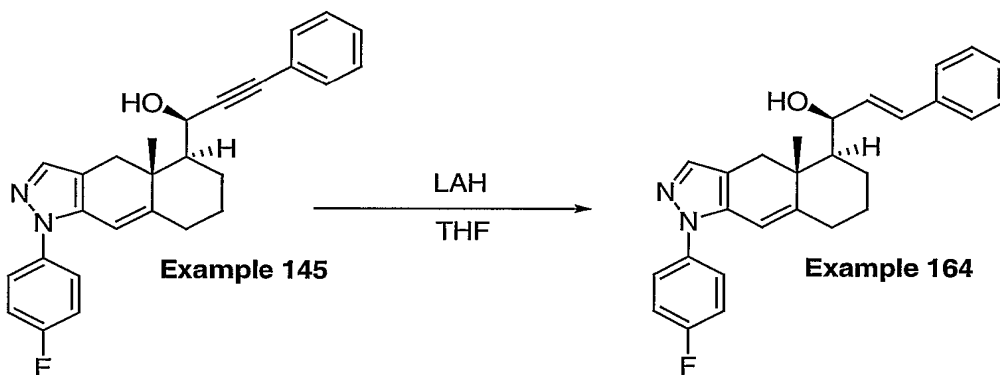
5

Compound	Molecular structure	LCMS (M+1) ⁺
160		380
161		430
162		394
163		382

EXAMPLE 164

5

Step 1.



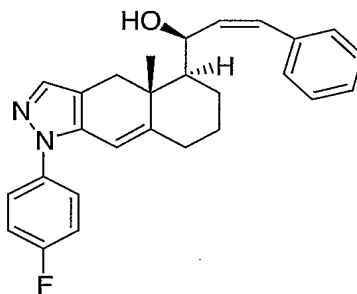
10

To a solution of **145** (7.4 mg, 0.018 mmol) in THF (1 mL) was added LAH (144 μL of a 1 M solution in Et_2O , 0.144 mmol). The reaction was stirred at room temperature for 24 hours and then added slowly to a mixture of $\text{Et}_2\text{O}/1\text{N HCl}$ (10/1, 20 mL). The mixture was washed with H_2O and brine (5 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (5 to 20% $\text{EtOAc}/\text{hexanes}$) afforded 4.5 mg (61%) of **164**. $R_f = 0.17$ (25% $\text{EtOAc}/\text{hexanes}$). LCMS = 415; $(\text{M}+1)^+$. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.45-7.47 (m, 2H), 7.43 (s, 1H), 7.40 (d, $J = 7.4$ Hz, 2H), 7.33 (t, $J = 7.7$ Hz, 2H), 7.25 (t, $J = 7.3$ Hz, 1H), 7.15 (t, $J = 8.5$ Hz, 2H), 6.62 (d, $J = 15.9$ Hz, 1H), 6.31 (dd, $J = 16.0, 5.4$ Hz, 1H), 6.12 (d, $J = 1.8$ Hz, 1H), 4.73 (d, $J = 5.0$ Hz, 1H), 3.09 (d, $J = 15.1$ Hz, 1H),

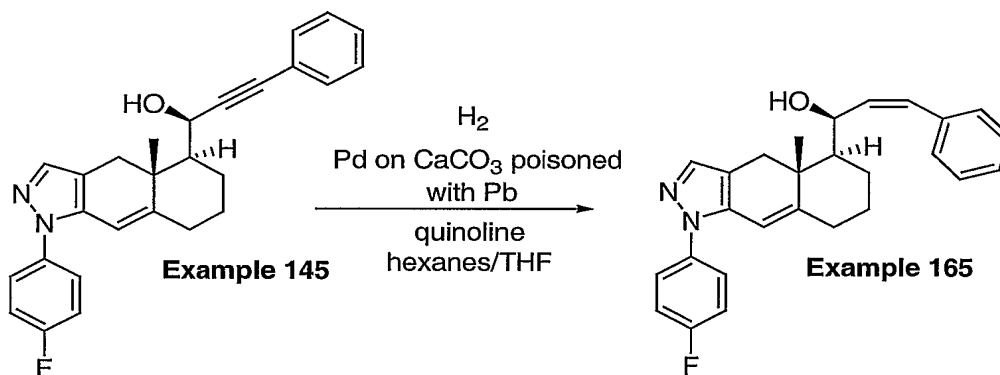
20

2.62 (d, $J = 15.1$ Hz, 1H), 2.42 (m, 1H), 2.32 (m, 1H), 1.91 (m, 1H), 1.79 (m, 1H), 1.67-1.72 (m, 2H), 1.38 (m, 1H), 1.22 (s, 3H).

5

EXAMPLE 165

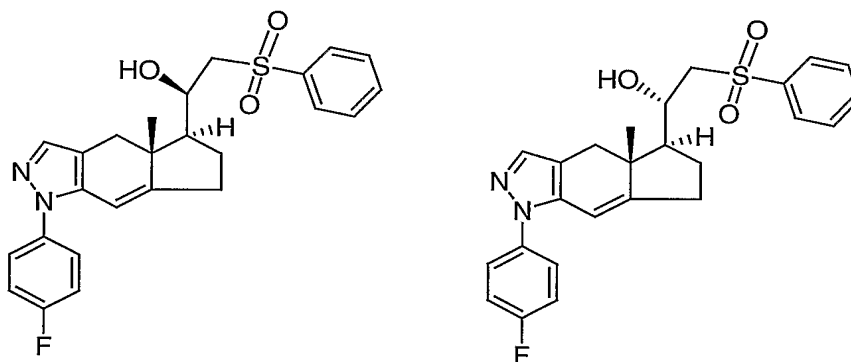
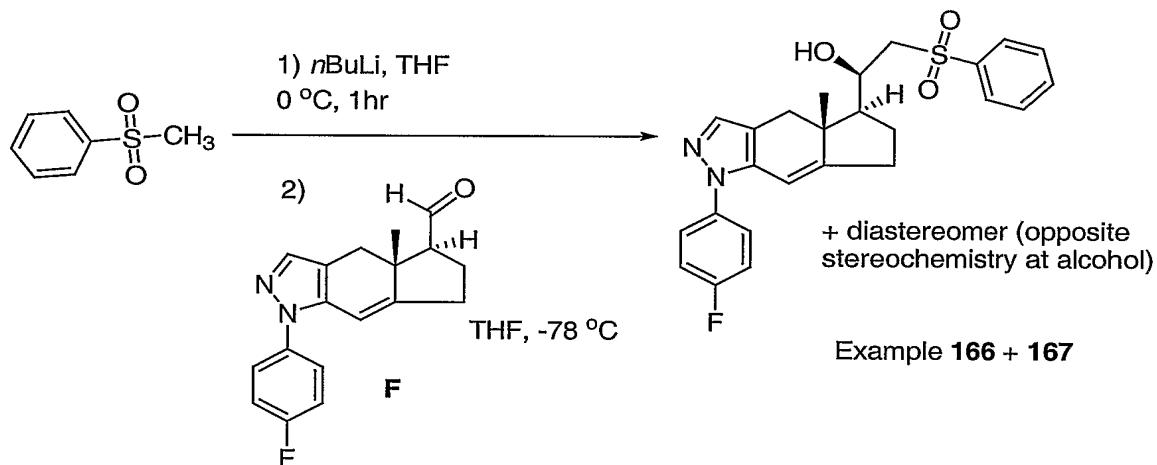
10 Step 1.



To a solution of **145** (12.9 mg, 0.031 mmol) in hexanes/THF (3/1; 1.6 mL) was added
 15 Pd on CaCO_3 poisoned with lead (4 mg) and quinoline (15 μL). The mixture was stirred at room temperature for 15 minutes and then placed under H_2 . The reaction was stirred at room temperature for 2 hours and then the catalyst was removed by filtration. The filtrate was diluted with EtOAc (35 mL), washed with 1 N HCl and brine (10 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*.
 20 Purification of the residue by flash chromatography (5 to 20% EtOAc/hexanes) afforded 7.3 mg (56%) of **165**. $R_f = 0.17$ (25% EtOAc/hexanes). LCMS = 415; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz) δ 7.38-7.44 (m, 4H), 7.32-7.35 (m, 4H), 7.14

(t, $J = 8.6$ Hz, 2H), 6.56 (d, $J = 11.7$ Hz, 1H), 6.08 (d, $J = 1.8$ Hz, 1H), 5.90 (dd, $J = 11.7, 9.0$ Hz, 1H), 4.91 (d, $J = 8.9$ Hz, 1H), 2.76 (d, $J = 15.2$ Hz, 1H), 2.29-2.42 (m, 3H), 1.88-1.96 (m, 2H), 1.77 (qd, $J = 9.6, 3.3$ Hz, 1H), 1.62 (dd, $J = 12.5, 2.4$ Hz, 1H), 1.41 (m, 1H), 1.10 (s, 3H).

5

Example 166+16710 Step 1: Addition of Lithium Phenyl Sulfone Reagent to Aldehyde **F**

15 A solution of methyl phenyl sulfone (285 mg, 1.83 mmol) in THF (16 mL) was cooled to 0°C and $n\text{BuLi}$ (950 μL of a 1.6 M solution in hexanes, 1.52 mmol) was added dropwise by syringe. The reaction was stirred at 0°C for 1 hour and then it was further cooled to -78°C. Aldehyde **F** (45.1 mg, 0.152 mmol) in THF (4 mL) was added by cannula. The reaction was stirred at -78 °C for 45 minutes. 1 mL of isopropyl alcohol was added at -78 °C and then the reaction was poured into saturated

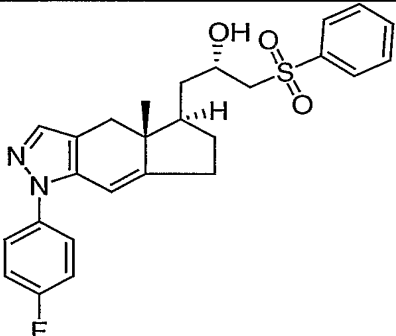
NH₄Cl (25 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10 to 50% EtOAc/hexanes) yielded a mixture of 2 diastereomers.

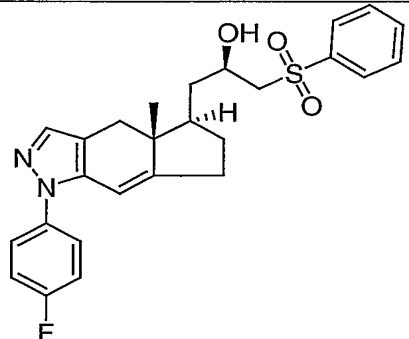
- 5 Further purification by PTLC (20/40/40 hexanes/CH₂Cl₂/Et₂O) afforded 24.4 mg (35%) of the less polar diastereomer and 11.3 mg (16%) of the more polar diastereomer.

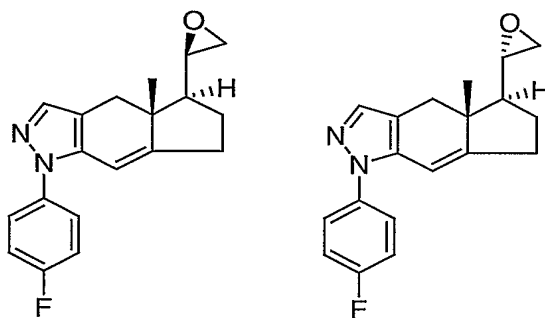
Less Polar diastereomer: $R_f = 0.32$ (50% EtOAc/hexanes). LCMS = 453; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 7.98 (d, $J = 7.8$ Hz, 2H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.61 (t, $J = 7.8$ Hz, 2H), 7.42 (m, 2H), 7.36 (s, 1H), 6.08 (s, 1H), 4.32 (m, 1H), 3.48 (s, 1H), 3.32 (m, 2H), 2.67 (d, $J = 15$ Hz, 1H), 2.57 (m, 1H), 2.51 (d, $J = 15$ Hz, 1H), 2.15 (s, 1H), 1.99 (m, 1H), 1.91 (m, 1H), 1.83 (m, 1H), 0.89 (s, 3H).

More Polar diastereomer: $R_f = 0.32$ (50% EtOAc/hexanes). LCMS = 453; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 7.95 (d, $J = 8.4$ Hz, 2H), 7.68 (m, 1H), 7.61 (t, $J = 9$ Hz, 2H), 7.45 (m, 2H), 7.38 (s, 1H), 7.13 (t, $J = 9$ Hz, 2H), 6.11 (s, 1H), 4.26 (m, 1H), 3.27 (s, 2H), 3.15 (d, $J = 19.2$ Hz, 2H), 2.63 (d, $J = 19.2$ Hz, 1H), 2.57 (m, 1H), 2.42 (m, 1H), 2.15 (s, 1H), 1.98 (m, 1H), 1.71 (m, 2H), 1.42 (m, 1H), 1.03 (s, 3H).

- 20 Starting from the appropriate aldehyde, the following compounds were synthesized following procedures analogous to those described for examples **166** and **167**:

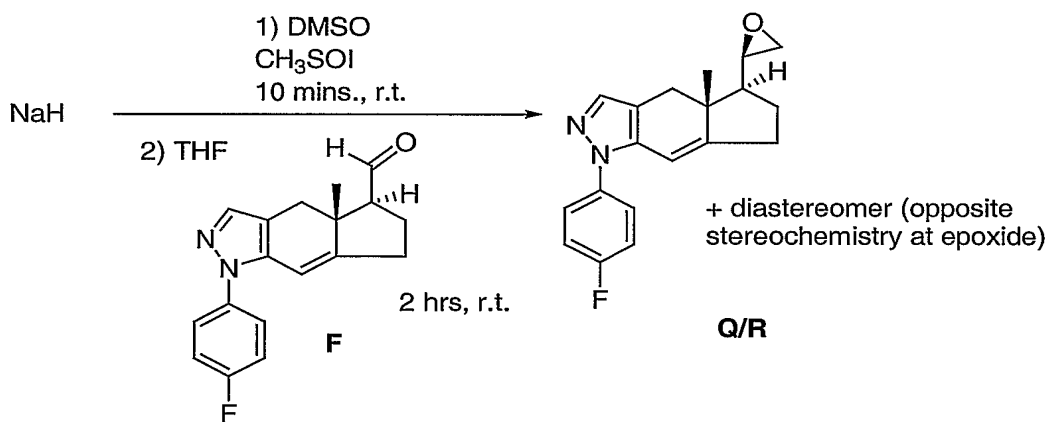
Compound	Molecular structure	LCMS (M+1) ⁺
168		467

169		467
-----	--	-----

Epoxide Q/R

5

Step 1:



10

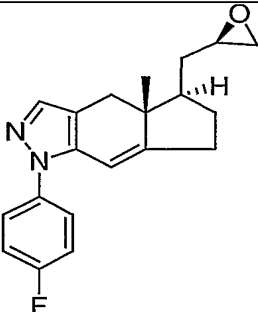
Trimethyl sulfoxonium iodide (240 mg, 1.09 mmol) was added as a solid to a suspension of sodium hydride (36.5 mg, 0.91 mmol of a 60% dispersion in mineral oil) in DMSO (2 mL). The reaction was stirred at room temperature for 10 minutes. Aldehyde **F** (54.0 mg, 0.18 mmol) in THF (4 mL) was added by cannula. The

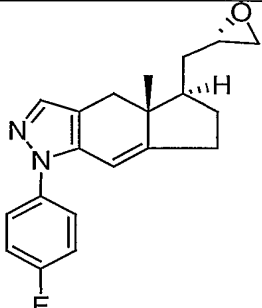
reaction was stirred at room temperature for 2 hours. 1 mL of water was added and then the reaction was poured into saturated NaHCO₃ (25 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 40% EtOAc/hexanes) yielded 8.8 mg (16%) of the less polar diastereomer and 11.2 mg (20%) of the more polar diastereomer.

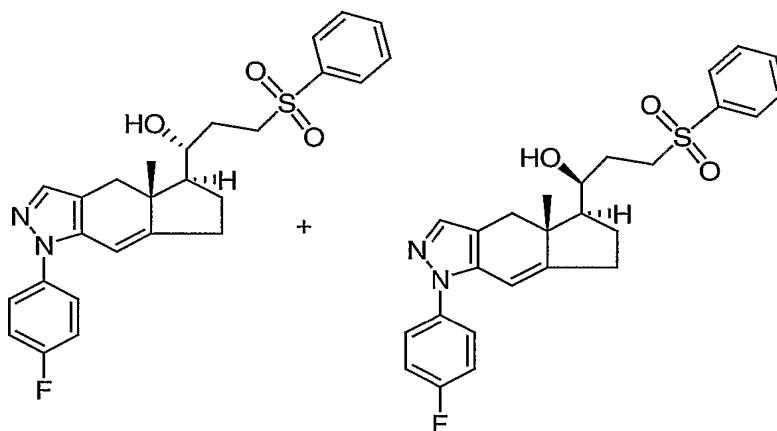
Less Polar diastereomer: $R_f = 0.56$ (50% EtOAc/hexanes). LCMS = 311; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 7.15 (m, 2H), 6.91 (s, 1H), 6.80 (t, $J = 8.7$ Hz, 2H), 5.85 (s, 1H), 2.56 (m, 1H), 2.44 (d, $J = 15.6$ Hz, 1H), 2.32 (m, 1H), 2.24 (m, 1H), 2.18 (d, $J = 15.6$ Hz, 1H), 2.12 (m, 1H), 2.02 (m, 1H), 1.45 (m, 2H), 1.31 (m, 1H), 0.63 (s, 3H).

More Polar diastereomer: $R_f = 0.52$ (50% EtOAc/hexanes). LCMS = 311; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 7.12 (m, 2H), 6.94 (s, 1H), 6.84 (t, $J = 8.7$ Hz, 2H), 5.82 (s, 1H), 2.50 (m, 1H), 2.47 (s, 1H), 2.79 (m, 1H), 2.17 (m, 2H), 2.07 (m, 2H), 1.44 (m, 2H), 1.19 (m, 1H), 0.67 (s, 3H).

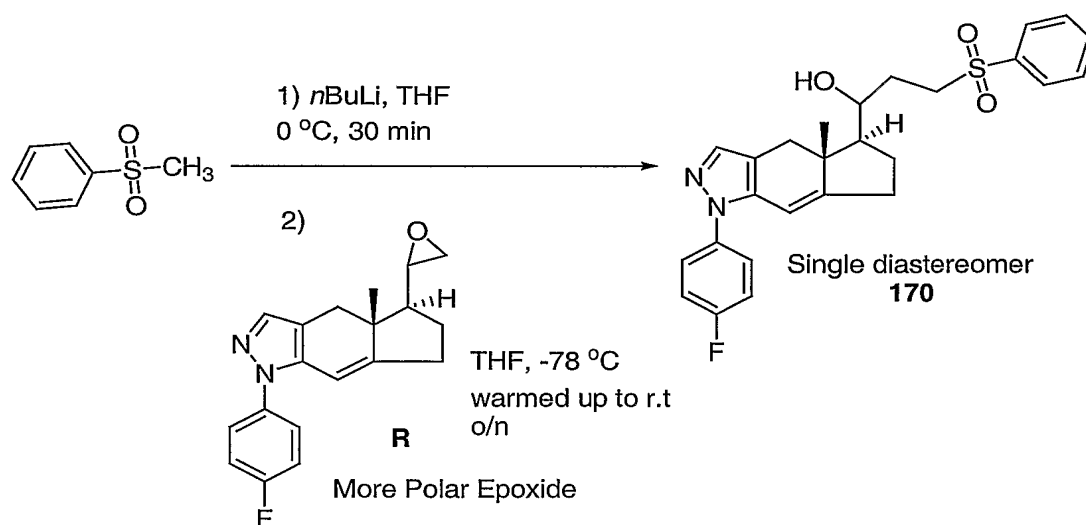
Starting from the appropriate aldehyde, the following compounds were synthesized following procedures analogous to those described for **Q/R**:

Compound	Molecular structure	LCMS (M+1) ⁺
S		326

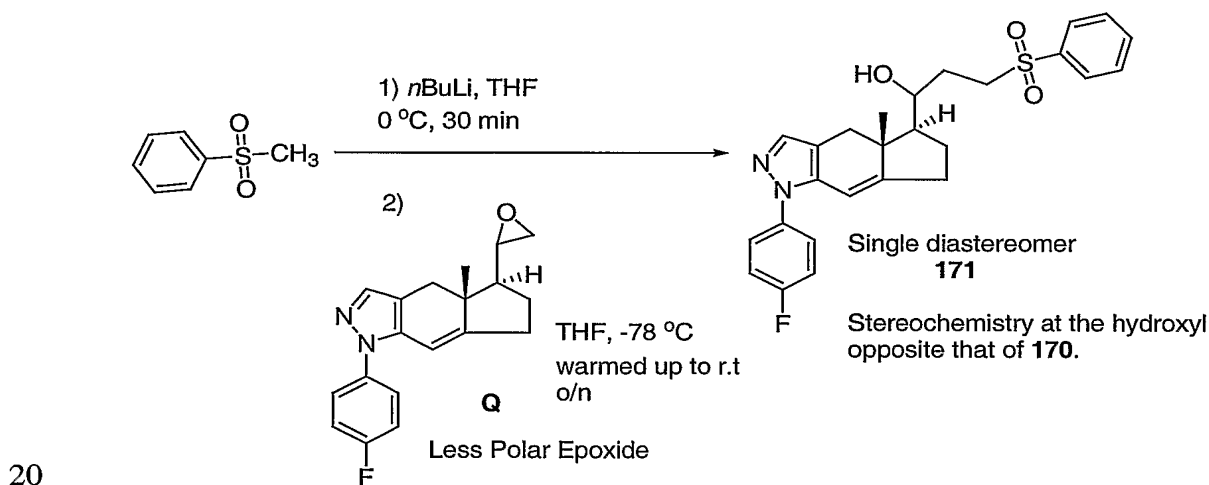
T		326
----------	---	-----

EXAMPLE 170 and 171

5

Step 1: Addition of Lithium Phenyl Sulfone Reagent to Epoxide **R**

A solution of methyl phenyl sulfone (305 mg, 1.92 mmol) in THF (12 mL) was cooled to 0 °C and *n*BuLi (1 mL of a 1.6 M solution in hexanes, 1.6 mmol) was added dropwise by syringe. The reaction was stirred at 0 °C for 30 min. and then cooled to -78 °C. Epoxide **R** (10 mg, 0.032 mmol) in THF (2 mL) was added by cannula. The reaction was stirred at -78 °C for 45 minutes. The reaction was warmed to room temperature and left at room temperature overnight. After stirring overnight at room temperature, 1 mL of isopropyl alcohol was added, and the reaction was poured into saturated NH₄Cl (10 mL). The mixture was extracted with EtOAc (25 mL) and the organic layer was washed with water and brine (10 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 100% EtOAc/hexanes) yielded a mixture of desired product and minor impurities. Further purification by PTLC (20/40/40 hexanes/CH₂Cl₂/Et₂O) afforded 4.9 mg (33%) of **170**. *R_f* = 0.17 (50% EtOAc/hexanes). LCMS = 467; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz): δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.45 (m, 2H), 7.37 (s, 1H), 7.13 (t, *J* = 8.1 Hz, 2H), 6.13 (s, 1H), 3.82 (t, *J* = 7.8 Hz, 1H), 3.29 (m, 2H), 3.05 (d, *J* = 15.6 Hz, 1H), 2.61 (m, 1H), 2.45 (m, 1H), 2.12 (m, 1H), 1.83 (m, 4H), 1.64 (m, 1H), 1.53 (m, 1H), 1.01 (s, 3H).



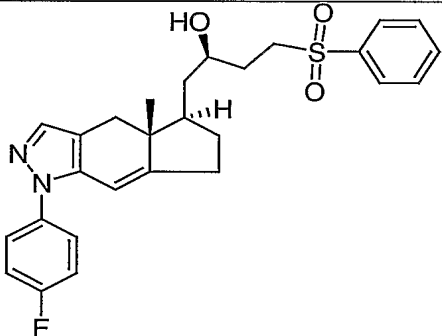
A solution of methyl phenyl sulfone (305 mg, 1.92 mmol) in THF (12 mL) was cooled to 0 °C and *n*BuLi (1 mL of a 1.6 M solution in hexanes, 1.6 mmol) was added dropwise by syringe. The reaction was stirred at 0 °C for 30 min and then cooled to -78 °C. Epoxide **Q** (10 mg, 0.032 mmol) in THF (2 mL) was added by

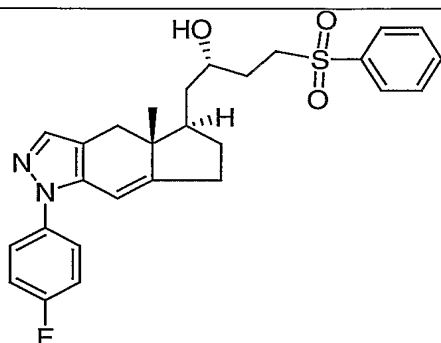
25

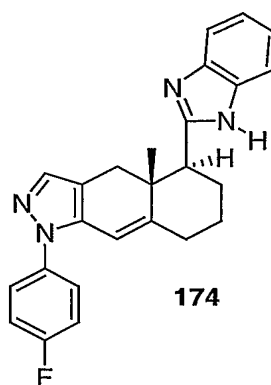
cannula. The reaction was stirred at -78°C for 45 minutes. The reaction was warmed to room temperature and left at room temperature overnight. After stirring overnight at room temperature, 1 mL of isopropyl alcohol was added and the reaction was poured into saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (25 mL) and the organic layer was washed with water and brine (10 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 100% EtOAc/hexanes) yielded a mixture of desired product and some minor impurities. Further purification by PTLC (20/40/40 hexanes/ CH_2Cl_2 /Et₂O) afforded 3.2 mg of example **171** (21%). $R_f = 0.17$ (50% EtOAc/hexanes). LCMS = 467; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 600 MHz): δ 7.96 (d, $J = 7.8$ Hz, 2H), 7.69 (m, 1H), 7.61 (m, 2H), 7.45 (m, 2H), 7.38 (s, 1H), 7.14 (t, $J = 7.8$ Hz, 2H), 6.12 (s, 1H), 3.87 (m, 1H), 3.34 (m, 2H), 2.75 (d, $J = 15.5$ Hz, 1H), 2.60 (m, 1H), 2.53 (d, $J = 15.5$ Hz, 1H), 2.43 (m, 1H), 2.14 (m, 1H), 1.89 (m, 1H), 1.81 (m, 3H), 0.96 (s, 3H).

15

Starting from the appropriate epoxide, the following compounds were synthesized following procedures analogous to those described for examples **170** and **171**:

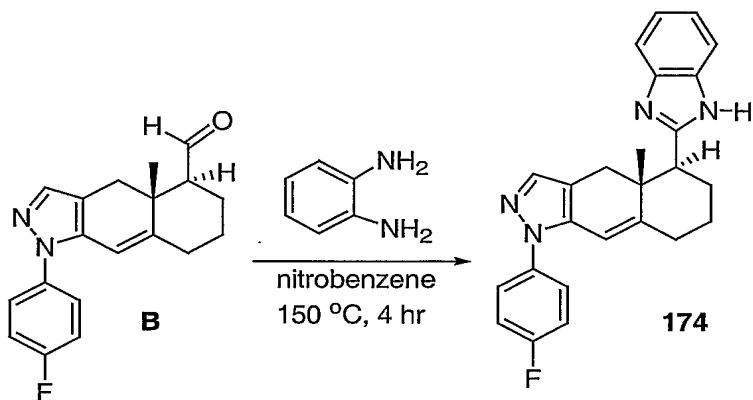
Compound	Molecular structure	LCMS $(\text{M}+1)^+$
172		481

173		481
-----	--	-----

Example 174

5

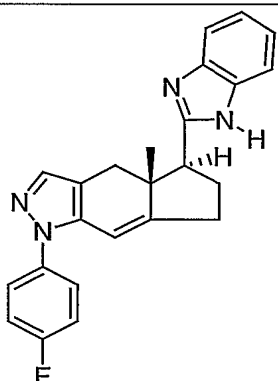
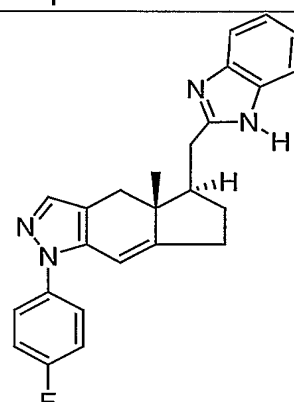
Step 1: Addition of 1,2 Phenylenediamine to aldehyde **B**.



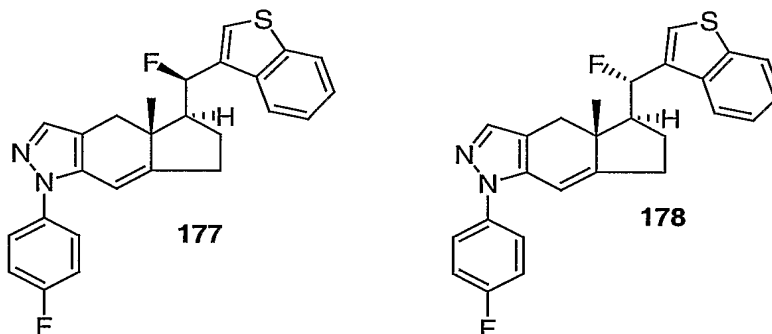
10

1,2 Phenylenediamine (10.5 mg, 0.097 mmol) and aldehyde **B** (15.0 mg, 0.05 mmol) were placed in a flask under nitrogen. Nitrobenzene (500 μ L) was added, and the reaction was heated to 150 °C. The reaction was stirred at 150 °C for 4 hours.

- After cooling to room temperature, the reaction was loaded directly onto silica gel and the column was eluted with 100% hexanes to remove the nitrobenzene, followed by 40 to 80% EtOAc/hexanes to afford a mixture of the desired product and some minor impurities. Further purification by PTLC (2/98 MeOH/CH₂Cl₂) gave 16.0 mg (84%) of example **174**: $R_f = 0.19$ (40% EtOAc/hexanes). LCMS = 399; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.55 (s, 1H), 7.39 (m, 2H), 7.26 (s, 1H), 7.20 (m, 2H), 7.11 (t, $J = 8.5$ Hz, 3H), 6.14 (s, 1H), 3.19 (m, 1H), 2.88 (d, $J = 15.5$ Hz, 1H), 2.63 (d, $J = 15.5$ Hz, 1H), 2.40 (m, 2H), 2.21 (m, 2H), 1.94 (m, 2H), 1.44 (m, 1H), 1.21 (s, 3H).
- 10 Starting from the appropriate aldehyde, the following compounds were synthesized following procedures analogous to those described for Benzimidazole **174**:

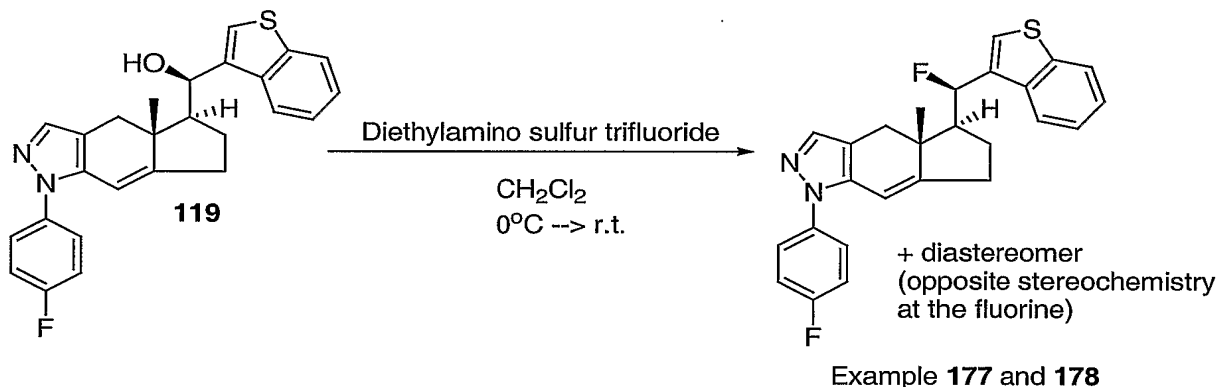
Compound	Molecular structure	LCMS (M+1) ⁺
175		385
176		399

5

EXAMPLE 177 and 178

Step 1. Addition of DAST to Example 119.

10



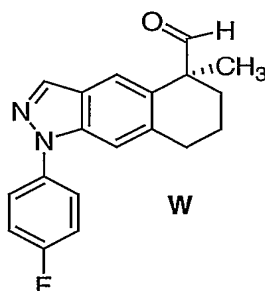
In a plastic vial, a solution of Example **119** (38.2 mg, 0.089 mmol) in CH_2Cl_2 (500 μL) was cooled to 0 $^\circ\text{C}$ and diethylamino sulfur trifluoride (23.6 μL , 0.178 mmol) was added dropwise by syringe. The reaction was stirred at 0 $^\circ\text{C}$ for 10 minutes and then was warmed to room temperature. The reaction was stirred at room temperature for 2 hours. The reaction was poured into saturated NaHCO_3 (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with brine (15 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 20%

EtOAc/hexanes) yielded a mixture of 2 diastereomers, which were separated using an OD chiral column (15% IPA/heptanes) to yield 4.6 mg (12%) of peak 1 and 6.9 mg (18%) of peak 2.

Peak 1: $R_f = 0.39$ (40% EtOAc/hexanes). LCMS = 433; $(M+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 8.00 (d, $J = 7.8$ Hz, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.48 (m, 2H), 7.46 (s, 1H), 7.15 (t, $J = 8.4$ Hz, 2H), 6.17 (s, 1H), 5.81 (dd, $J = 47.4$ Hz, 10.8 Hz, 1H), 3.21 (dd, $J = 15.9$ Hz, 3.9 Hz, 1H), 2.88 (d, $J = 16.2$ Hz, 1H), 2.80 (m, 1H), 2.59 (m, 1H), 2.40 (m, 1H), 1.59 (m, 1H), 1.48 (m, 1H), 1.26 (s, 3H).

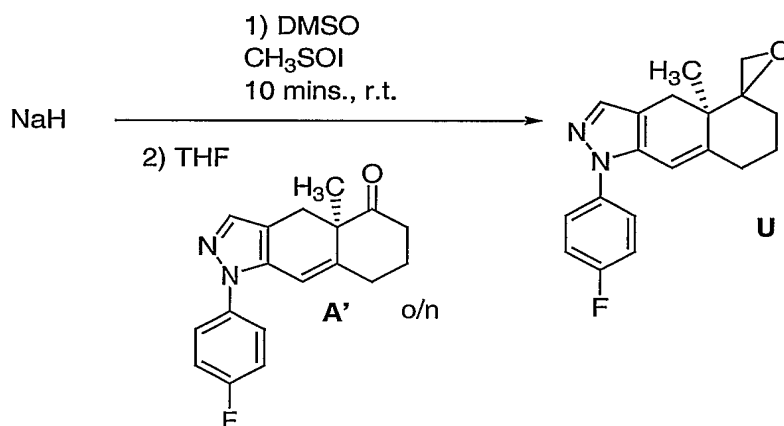
Peak 2: $R_f = 0.44$ (40% EtOAc/hexanes). LCMS = 433; $(M+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.92 (d, $J = 1.8$ Hz, 1H), 7.89 (d, $J = 2.4$ Hz, 1H), 7.49 (d, $J = 1.8$ Hz, 1H), 7.41 (m, 4H), 7.14 (t, $J = 9$ Hz, 2H), 6.14 (t, $J = 1.8$ Hz, 1H), 5.91 (dd, $J = 46.8$ Hz, 6.6 Hz, 1H), 2.69 (m, 2H), 2.47 (m, 1H), 2.88 (dd, $J = 38.7$ Hz, 15 Hz, 2H), 2.17 (m, 1H), 1.21 (d, $J = 6$ Hz, 1H), 1.15 (s, 3H).

15

Aldehyde W

Step 1:

20

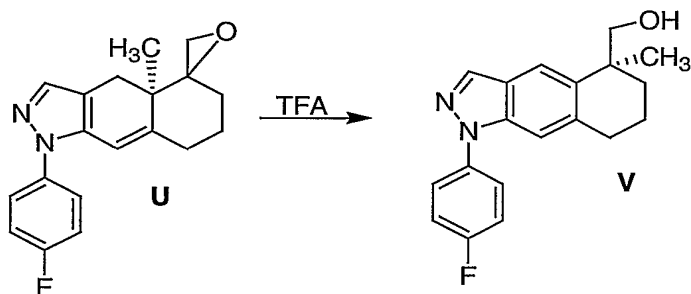


Trimethyl sulfoxonium iodide (334 mg, 1.52 mmol) was added as a solid to a suspension of sodium hydride (54 mg, 1.35 mmol of a 60% dispersion in mineral oil) in DMSO (4 mL). The reaction was stirred at room temperature for 10 minutes.

5 Ketone A (100 mg, 0.338 mmol) in THF (0.5 mL) was added by cannula. The reaction was stirred at room temperature overnight. 1 mL of water was added and then the reaction was poured into saturated NaHCO_3 (25 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*.

10 Purification by flash chromatography (5 to 40% EtOAc/hexanes) afforded 101.6 mg (97%) of U. $R_f = 0.56$ (40% EtOAc/hexanes). LCMS = 311; $(M+1)^+$.

Step 2:



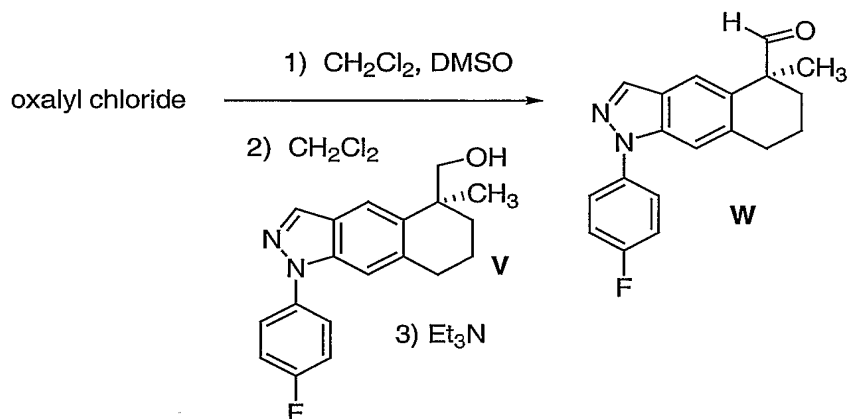
15

Trifluoroacetic acid (1.5 mL) was added to epoxide U (101.6 mg, 0.322 mmol). This reaction was stirred at room temperature for 20 minutes. The reaction was then poured into ice/ H_2O and neutralized with 10 % K_2CO_3 . The mixture was extracted with EtOAc (20 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*.

20 Purification by flash chromatography (5 to 40% EtOAc/hexanes) afforded 59.1 mg (58%) of V. $R_f = 0.42$ (50% EtOAc/hexanes). LCMS = 311; $(M+1)^+$. ^1H NMR (CDCl_3 , 600 MHz): δ 7.29 (s, 1H), 7.64 (s, 1H), 7.51 (m, 2H), 7.16 (s, 1H), 7.12 (t, $J = 8.4$ Hz, 2H), 3.69 (d, $J = 10.8$ Hz, 1H), 3.45 (d, $J = 10.8$ Hz, 1H), 2.82 (m, 2H), 1.96 (m, 1H), 1.75 (m, 2H), 1.52 (m, 1H), 1.24 (m, 3H).

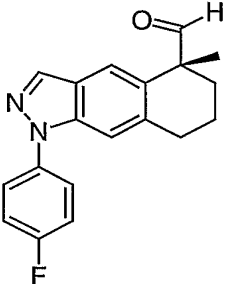
25

Step 3:



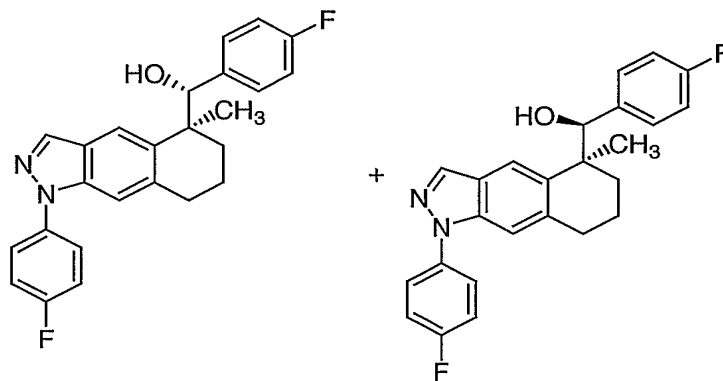
- 5 A solution of oxalyl chloride (75.4 μL , 0.86 mmol) in CH_2Cl_2 (4 mL) was cooled to -78°C . DMSO (122.7 μL , 1.73 mmols) was added. This reaction was stirred at room temperature for 10 minutes. Alcohol **V** (53.6 mg, 0.173 mmol) was dissolved in CH_2Cl_2 (1 mL) and added to the reaction via cannula. This was stirred at -78°C for 20 minutes. (482.0 μL , 3.46 mmol) of triethyl amine was added at -78°C and then
- 10 the reaction was warmed to room temperature. The mixture was extracted with EtOAc (20 mL) and the organic layer was washed with water, 1N HCl, NaHCO_3 , and brine (15 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 50% EtOAc/hexanes) afforded 39.8 mg (75%) of **W**. $R_f = 0.69$ (50% EtOAc/hexanes).
- 15 LCMS = 309; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 600 MHz): δ 9.55 (s, 1H), 8.11 (s, 1H), 7.66 (m, 2 H), 7.53 (s, 1H), 7.44 (s, 1H), 7.23 (t, $J = 8.4$ Hz, 2H), 2.97 (m, 2H), 2.19 (m, 1H), 1.91 (m, 2 H), 1.74 (m, 1H), 1.54 (m, 3H).

The following compound was synthesized following procedures analogous to those described for Aldehyde **W** starting from ketone **A**:

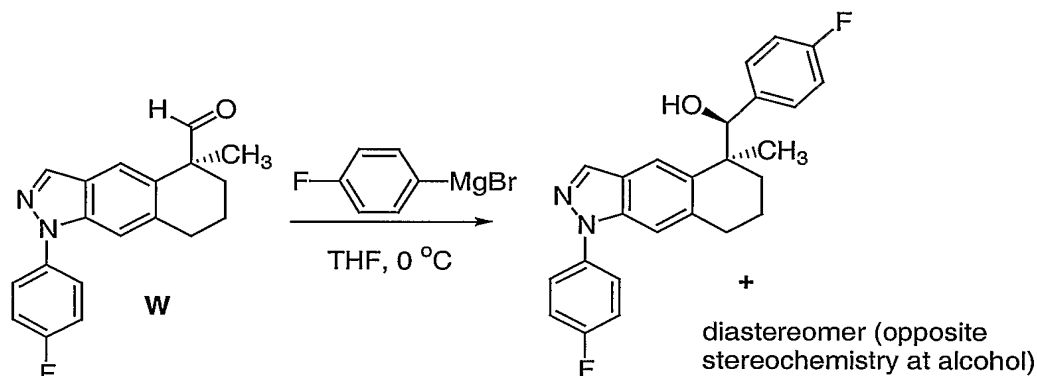
Compound	Molecular structure	LCMS (M+1) ⁺
X		309

5

EXAMPLE 179 and 180



10

Step 1: Addition of Grignard Reagent to Aldehyde **W**Example **179** and **180**

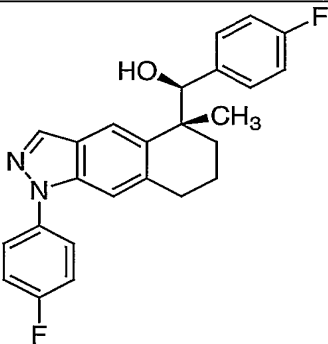
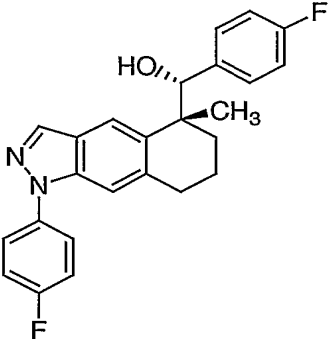
5

Aldehyde **W** (38.2 mg, 0.121 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. 4-fluorobenzyl magnesium bromide (310 μ L of a 2.0 M solution in diethyl ether, 0.620 mmol) was added dropwise by syringe. The reaction was stirred at 0 °C for 1 hour and then quenched with saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (40 mL) and the organic layer was washed with H_2O and brine (10 mL each), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 80% EtOAc/hexanes) yielded a mixture of 2 diastereomers, which were separated on an AD chiral column (30% IPA/heptanes) to afford 24.4 mg (49%) of peak 1 and 17.2 mg (34%) of peak 2.

15 Peak 1: $R_f = 0.11$ (25% EtOAc/hexanes). LCMS = 405; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 8.03 (s, 1H), 7.83 (s, 1H), 7.56 (m, 2H), 7.15 (t, $J = 8.5$ Hz, 2H), 7.09 (m, 2H), 7.16 (s, 1H), 6.86 (t, $J = 8.8$ Hz, 2H), 4.76 (s, 1H), 2.72 (m, 2H), 2.43 (s, 1H), 1.97 (s, 1H), 1.74 (m, 2H), 1.46 (m, 1H), 1.35 (s, 3H).

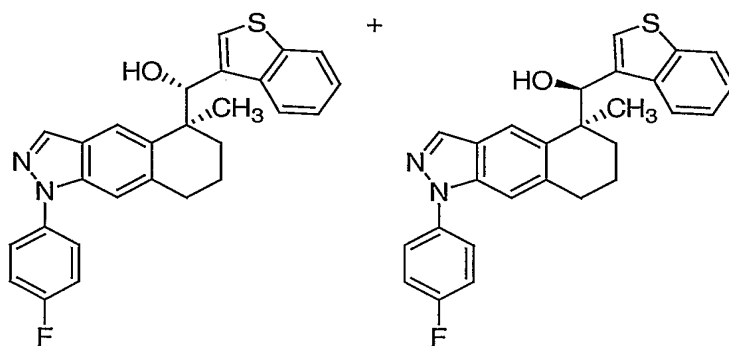
20 Peak 2: $R_f = 0.11$ (25% EtOAc/hexanes). LCMS = 405; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.95 (s, 1H), 7.69 (s, 1H), 7.51 (m, 2H), 7.16 (s, 1H), 7.17 (m, 2H), 7.09 (m, 2H), 6.86 (t, $J = 8.8$ Hz, 2H), 4.95 (s, 1H), 2.78 (m, 2H), 2.03 (m, 1H), 1.97 (s, 1H), 1.72 (s, 1H), 1.52 (m, 2H), 1.11 (s, 3H).

The following compounds were synthesized following procedures analogous to those described for Examples 179 and 180 and starting from Aldehyde X:

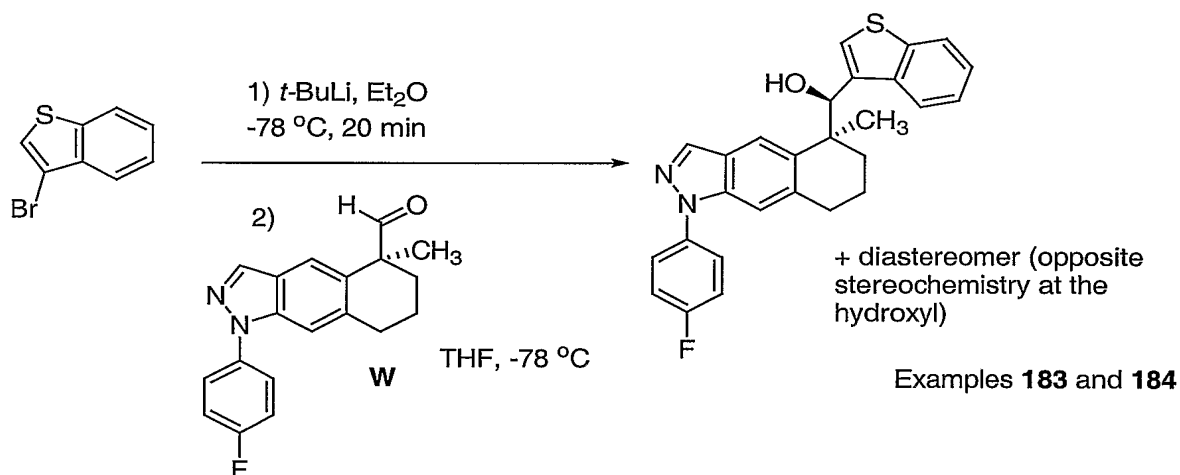
Compound	Molecular structure	LCMS (M+1) ⁺
181		405
182		405

5

EXAMPLE 183 and 184



10 Step 1: Addition of Aryl Lithium to Aldehyde W

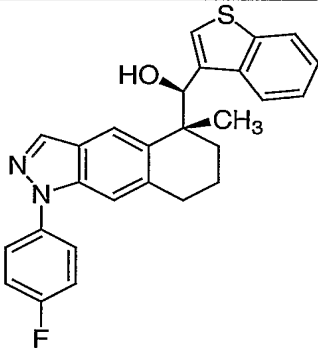
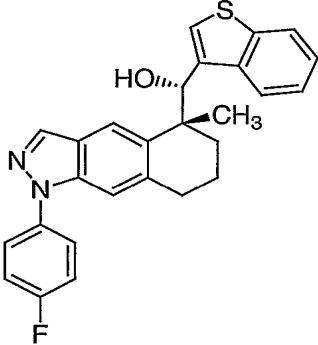


A solution of 3-bromothiophene (162.2 μ L, 1.24 mmol) in Et₂O (16 mL) was cooled to -78 °C and *t*-BuLi (1.45 mL of a 1.7 M solution in pentanes, 2.48 mmol) was added dropwise by syringe. The reaction was stirred at -78 °C for 20 minutes and then aldehyde **W** (38.2 mg, 0.124 mmol) in THF (2 mL) was added by cannula. The reaction was stirred at -78 °C for 45 minutes. 1 mL of isopropyl alcohol was added at -78 °C and the reaction was poured into saturated NH₄Cl (10 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 20% EtOAc/hexanes) yielded a mixture of 2 diastereomers that were separated using an AD chiral column (25% IPA/ heptanes) to yield 3.8 mg (6.9%) of Peak 1 and 6.7 mg (12%). Peak 2:

Peak 1: R_f = 0.74 (40% EtOAc/hexanes). LCMS = 443; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 8.01 (s, 1H), 7.90 (s, 1H), 7.83 (m, 1H), 7.73 (m, 1H), 7.55 (m, 1H), 7.16 (s, 1H), 7.19 (m, 2H), 5.23 (s, 1H), 2.72 (m, 2H), 2.09 (s, 1H), 1.93 (s, 1H), 1.83 (m, 1H), 1.61 (m, 1H), 1.45 (s, 3H).

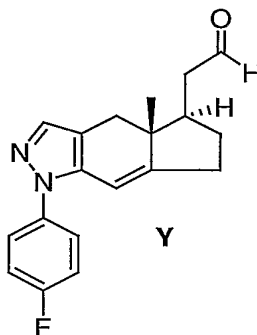
Peak 2: R_f = 0.74 (40% EtOAc/hexanes). LCMS = 443; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.90 (s, 1H), 7.78 (s, 1H), 7.69 (m, 1H), 7.64 (m, 1H), 7.51 (m, 1H), 7.20 (s, 1H), 7.14 (m, 2H), 7.08 (s, 1H), 7.07 (t, J = 9.0 Hz, 2H), 5.47 (s, 1H), 2.73 (t, J = 6.3 Hz, 1H), 2.17 (m, 1H), 1.93 (s, 1H), 1.79 (m, 1H), 1.57 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.21 (s, 3H).

The following compounds were synthesized following procedures analogous to those described for Examples 183 and 184 and starting from aldehyde X:

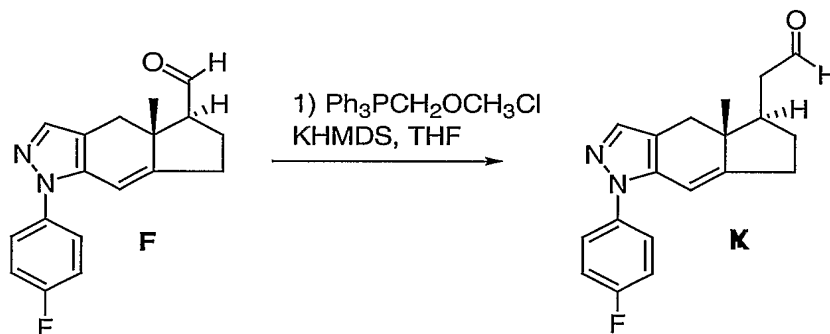
Compound	Molecular structure	LCMS (M+1) ⁺
185		443
186		443

5

ALDEHYDE Y



Step 1:



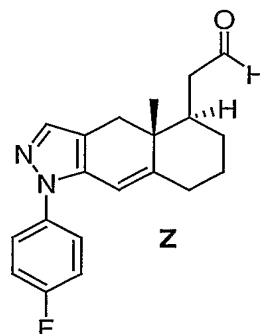
5

A suspension of (methoxymethyl)triphenylphosphonium chloride (763 mg, 2.2 mmol) in THF (8 mL) was cooled to 0 °C. Potassium bis(trimethylsilyl amide) (3.6 mL of a 0.5 M solution in toluene, 1.78 mmol) was added dropwise by syringe and the reaction turned bright orange/red. Next, a solution of aldehyde **F** (132 mg, 0.44 mmol) in THF (4 mL) was added by cannula. The reaction was allowed to warm to room temperature. After stirring at room temperature for 2 hours, 4N HCl was added slowly and the reaction was left stirring for another hour. The reaction was then diluted with EtOAc (50 mL), quenched with NaHCO_3 (50 mL), and washed with H_2O and brine (25 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 35% EtOAc/hexanes) to afford 95.1 mg (69%) of **Y**. $R_f = 0.29$ (25% EtOAc/hexanes). LCMS = 311; $(M + 1)^+$. ^1H NMR (CDCl_3 , 600 MHz) δ 9.86 (t, $J = 2.1$ Hz, 1H), 7.44–7.47 (m, 2H), 7.39 (s, 1H), 7.13–7.16 (m, 1H), 6.17 (s, 1H), 2.68 (d, $J = 15.0$ Hz, 1H), 2.60 (m, 2H), 2.55 (d, $J = 15.0$ Hz, 1H), 2.46 (m, 2H), 2.34 (m, 1H), 2.10 (m, 1H), 1.58 (m, 2H), 0.93 (s, 3H).

10

15

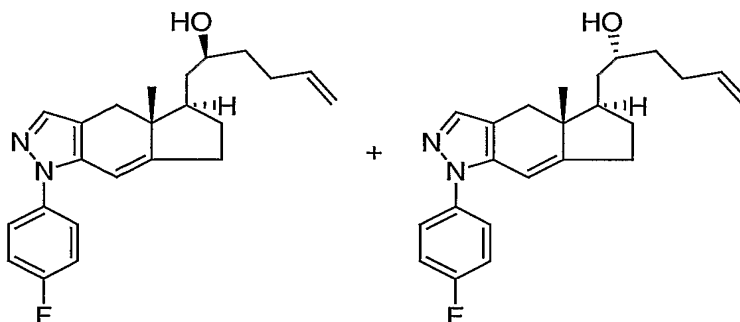
20

ALDEHYDE Z

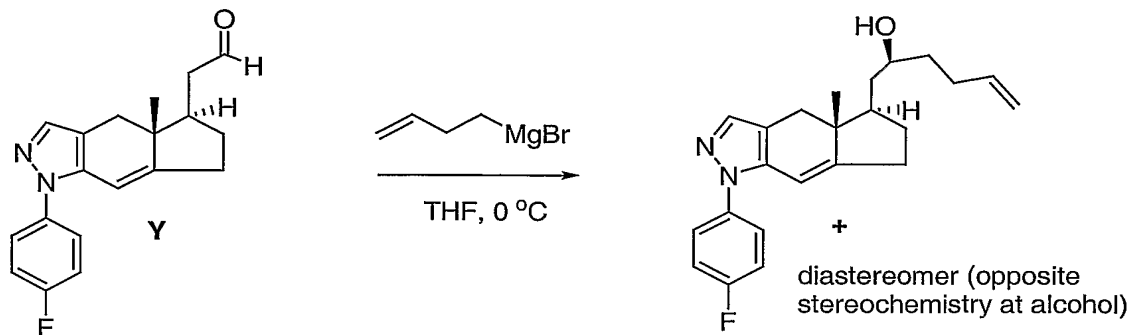
5 Aldehyde **Z** was synthesized from aldehyde **B** using the same procedure as was used in the synthesis of aldehyde **Y**.

EXAMPLE 187 and 188

10



Step 1: Addition of Grignard Reagent to Aldehyde **Y**



15

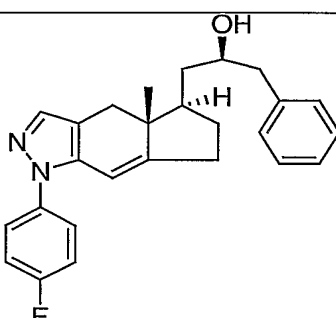
Example **187** and **188**

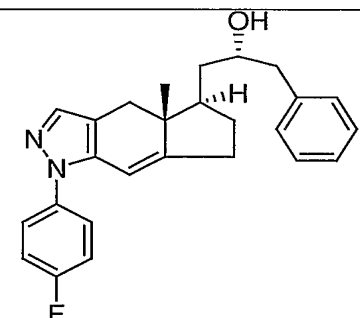
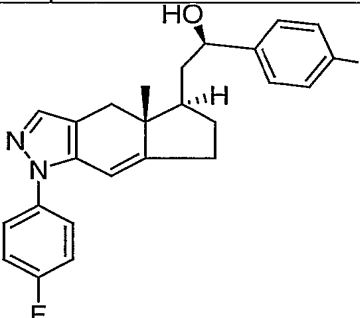
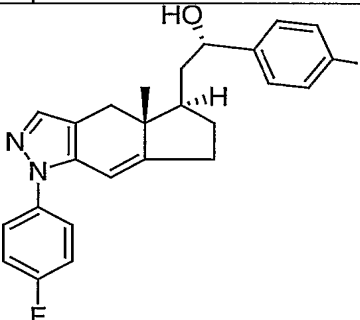
Aldehyde **Y** (53.0 mg, 0.17 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. 3-butenyl magnesium chloride (1.7 mL of a 0.5 M solution in THF, 0.85 mmol) was added dropwise by syringe. The reaction was stirred at 0 °C for 1 hour and then 1 mL of isopropyl alcohol was added. The reaction was then poured into saturated NH₄Cl (25mL) and extracted with EtOAc (40 mL). The organic layer was washed with H₂O and brine (25 mL each), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The two diastereomeric products were isolated by flash chromatography (5 to 20% EtOAc/hexanes) to afford 17.3 mg (28%) of the less polar diastereomer and 19.9 mg (32%) of the more polar diastereomer. Less Polar diastereomer: $R_f = 0.15$ (25% EtOAc/hexanes). LCMS = 366; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.44-7.47 (m, 2H), 7.33 (m, 2H), 7.30 (s, 1H), 7.01(m, 1H), 5.73 (m, 1H), 4.95(m, 1H), 4.87 (dd, $J = 8.5, 1.8$ Hz, 1H), 4.86 (d, $J = 10.3$ Hz, 2H), 3.63 (m, 1H), 2.62 (d, $J = 15.5$ Hz, 1H), 2.47 (m, 1H), 2.42 (d, $J = 7.5$ Hz, 1H), 2.07 (m, 2H), 1.92 (m, 1H), 1.74 (m, 1H), 1.38-1.56 (m, 6H), 0.80 (s, 3H).

More Polar diastereomer: $R_f = 0.14$ (25% EtOAc/hexanes). LCMS = 366; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.45 (m, 2H), 7.38 (m, 2H), 7.30 (s, 1H), 7.12 (m, 2H), 6.12 (m, 1H), 5.85 (m, 2H), 5.07(m, 1H), 4.99 (dd, $J = 8.5, 1.8$ Hz, 1H), 3.69 (m, 1H), 2.72 (d, $J = 15.5$ Hz, 1H), 2.57 (m, 1H), 2.51 (d, $J = 15.5$ Hz, 1H), 2.51 (m, 1H), 2.41 (m, 1H), 2.19 (m, 2H), 2.07 (m, 2H), 1.61-1.39 (m, 6H), 0.90 (s, 3H).

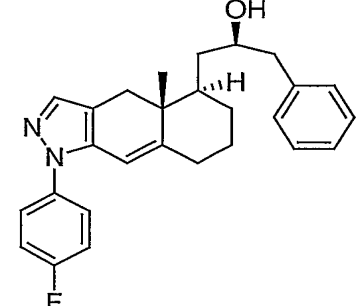
The following compounds were synthesized following procedures analogous to those described for examples **187** and **188**:

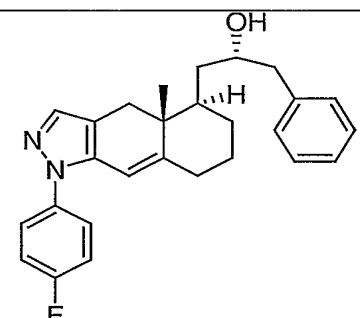
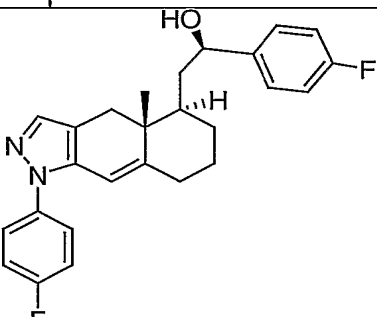
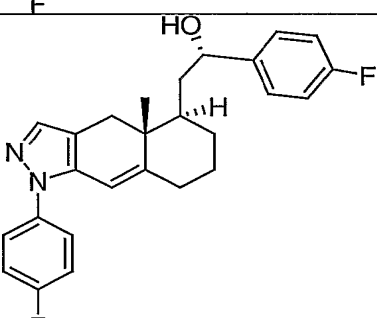
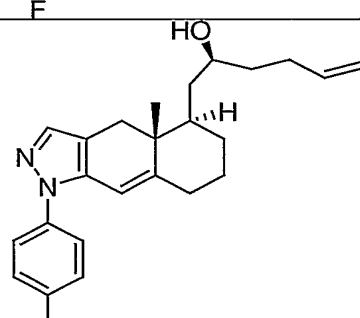
25

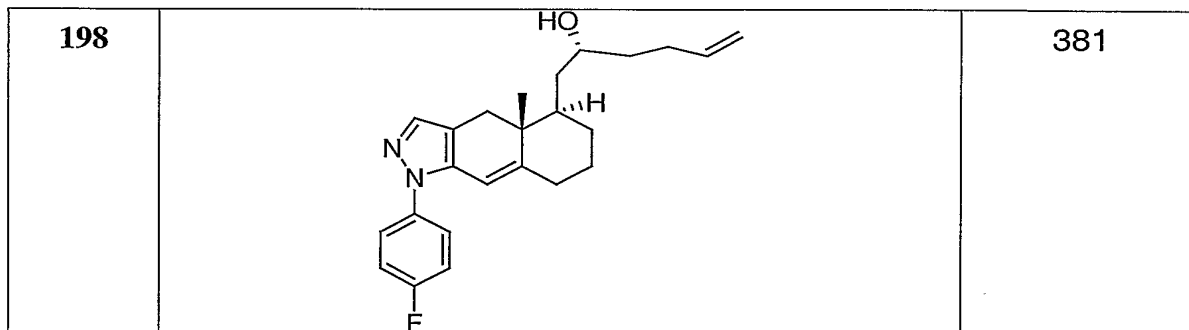
Compound	Molecular structure	LCMS (M+1) ⁺
189		403

190		403
191		407
192		407

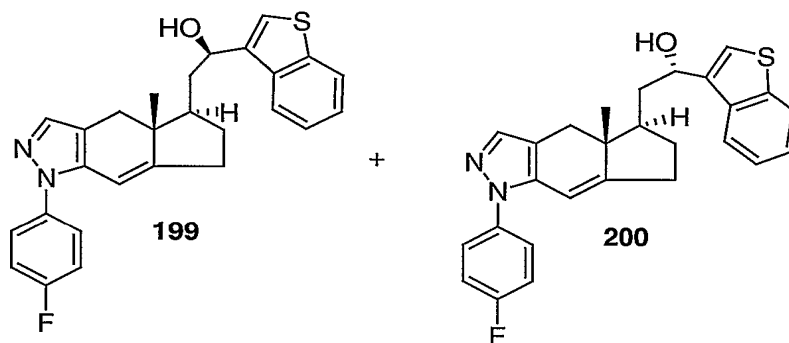
The following compounds were synthesized following procedures analogous to those described for examples **187** and **188** and starting from aldehyde **Z**:

Compound	Molecular structure	LCMS (M+1) ⁺
193		417

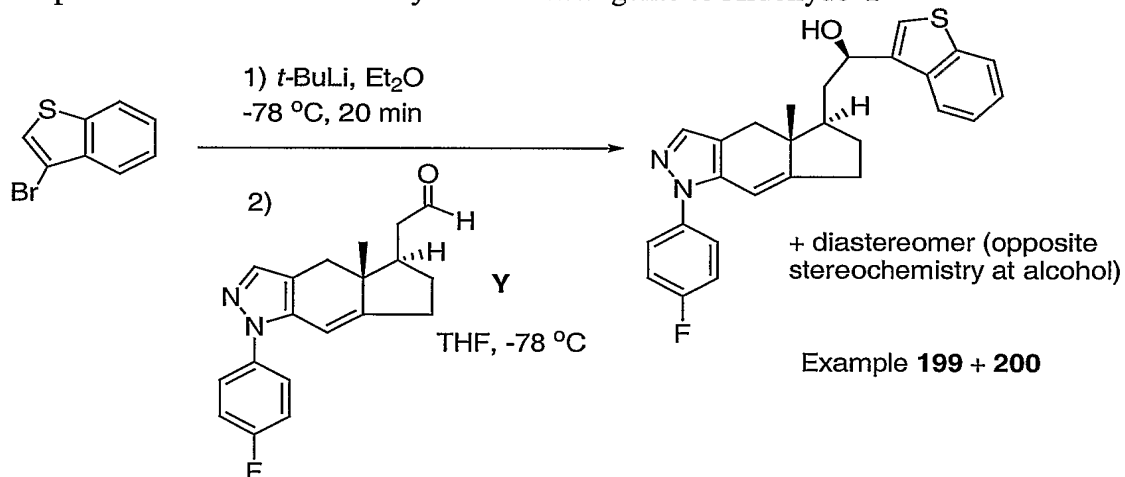
194		417
195		421
196		421
197		381

EXAMPLE 199 and 200

5



Step 1:

Addition of Aryl Lithium Reagents to Aldehyde **Y**

10

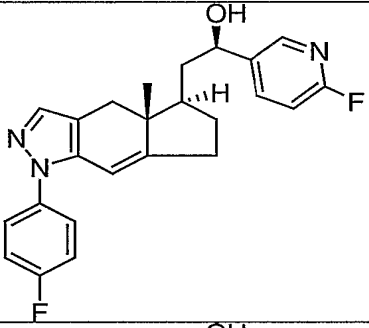
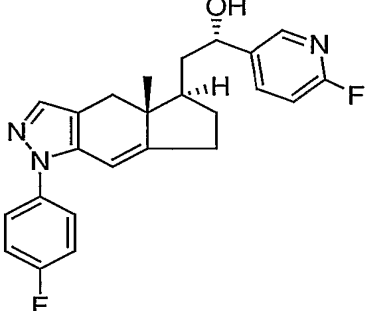
A solution of 1-Bromothianaphene (259 μ L, 1.98 mmol) in Et₂O (8 mL) was cooled to -78°C and *t*-BuLi (2.3 mL of a 1.7 M solution in pentanes, 3.95 mmol) was added dropwise by syringe. The reaction was stirred at -78°C for 20 minutes and then aldehyde Y (61.3 mg, 0.20 mmol) in THF (2 mL) was added by cannula. The reaction
5 was stirred at -78°C for 45 minutes. 1 mL of isopropyl alcohol was added at -78°C and then the reaction was poured into saturated NH₄Cl (25 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 to 20% EtOAc/hexanes) yielded a
10 mixture of 2 diastereomers. Further purification by PTLC (40/40/20 hexanes/CH₂Cl₂/Et₂O) afforded 34.7 mg of the less polar diastereomer contaminated with minor impurities and 28.2 mg (32%) of the more polar diastereomer. Final purification of the less polar diastereomer using an AD Chiral Column (35% isopropyl alcohol/heptanes) afforded 22.3 mg (25%) of the less polar diastereomer.

15 Less Polar diastereomer: $R_f = 0.21$ (25% EtOAc/hexanes). LCMS = 445; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.86 (d, $J = 8\text{ Hz}$, 1H), 7.80 (d, $J = 7.5\text{ Hz}$, 1H), 7.33 (m, 3H), 7.29 (s, 1H), 7.20 (s, 1H), 7.02 (m, 2H), 6.00 (s, 1H), 5.09 (t, $J = 6.5\text{ Hz}$, 1H), 2.64 (d, $J = 15\text{ Hz}$, 1H), 2.48 (m, 1H), 2.33 (d, $J = 15\text{ Hz}$, 1H), 2.70 (m, 1H), 2.13 (m, 1H), 1.97 (m, 1H), 1.87 (m, 1H), 1.73 (m, 1H), 1.52 (m, 1H),
20 1.18 (m, 1H), 0.86 (s, 3H).

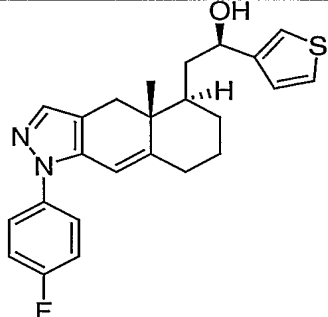
More Polar diastereomer: $R_f = 0.21$ (25% EtOAc/hexanes). LCMS = 445; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (t, $J = 6\text{ Hz}$, 2H), 7.34-7.45 (m, 6H), 7.13 (t, $J = 6.25\text{ Hz}$, 2H), 6.13 (s, 1H), 5.16 (d, $J = 6.5\text{ Hz}$, 1H), 2.73 (d, $J = 12.5\text{ Hz}$, 1H), 2.59 (m, 1H), 2.54 (d, $J = 12.5\text{ Hz}$, 1H), 2.46 (m, 1H), 2.17 (m, 2H),
25 2.05 (m, 1H), 1.86 (m, 1H), 1.59 (m, 1H), 1.25 (m, 1H), 0.90 (s, 3H).

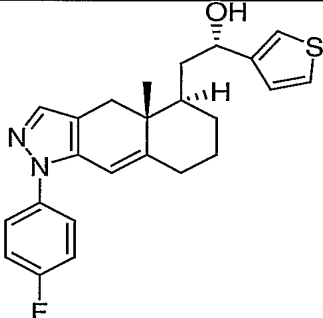
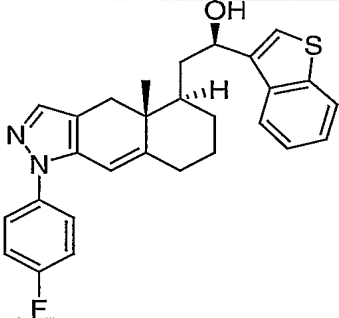
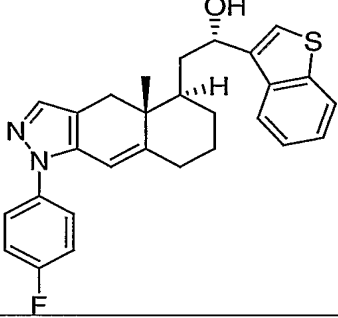
The following compounds were synthesized following procedures analogous to that described for Examples **199** and **200**:

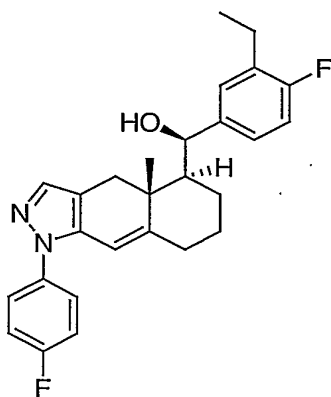
5

Compound	Molecular structure	LCMS (M+1) ⁺
201		408
202		408

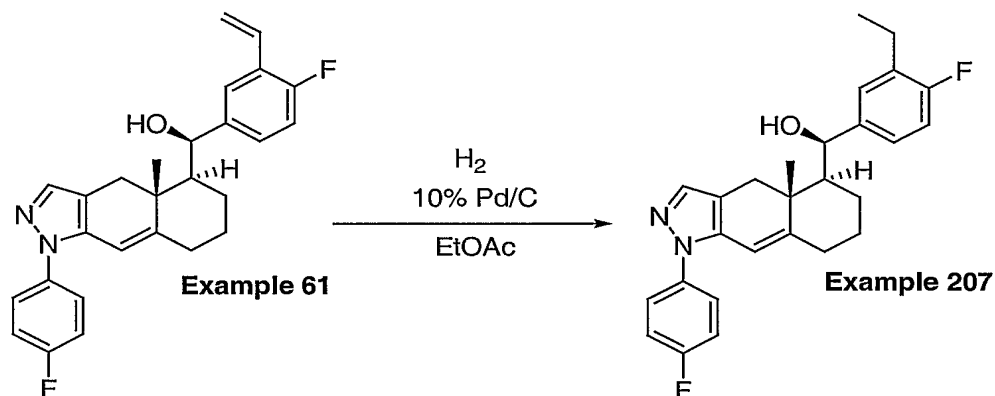
The following compounds were synthesized starting from aldehyde **Z** and following procedures analogous to that described for Examples **199** and **200**:

Compound	Molecular structure	LCMS (M+1) ⁺
203		409

204		409
205		459
206		459

EXAMPLE 207

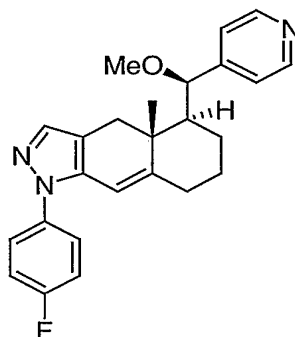
Step 1



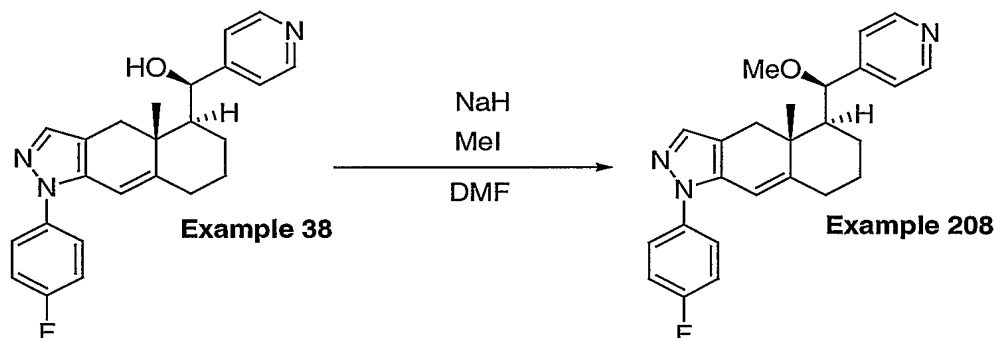
5 Example **61** (4.3 mg, 0.01 mmol) was dissolved in EtOAc (0.5 mL) and 10% Pd on activated carbon (1.0 mg) was added. The reaction was placed under H₂ and stirred at room temperature for 45 minutes. The catalyst was removed by filtration. The filtrate was concentrated, and the residue was purified by preparatory thin layer chromatography (25% EtOAc/hexanes) to afford 2.8 mg (65%) of Example

10 **207**. $R_f = 0.15$ (25% EtOAc/hexanes). LCMS = 435; (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz) δ 7.45-7.47 (m, 3H), 7.12-7.17 (m, 4H), 6.98 (t, $J = 8.4$ Hz, 1H), 6.12 (s, 1H), 5.16 (s, 1H), 3.18 (d, $J = 15$ Hz, 1H), 2.75 (d, $J = 15$ Hz, 1H), 2.65-2.70 (m, 2H), 2.41 (m, 1H), 2.28 (d, $J = 15$ Hz, 1H), 1.59-1.83 (m, 5H), 1.26 (s, 3H), 1.24 (t, $J = 7.8$ Hz, 3H).

15

EXAMPLE 208

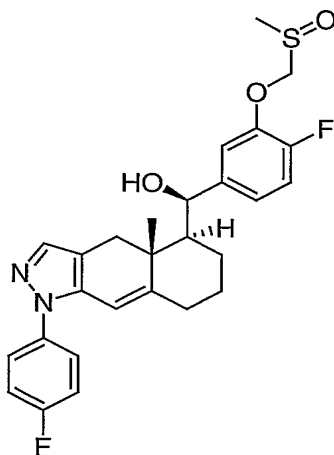
Step 1



- 5 Example **38** (11.6 mg, 0.03 mmol) was dissolved in EtOAc (2 mL) and NaH (10 mg, 0.42 mmol) was added. The reaction was stirred at room temperature for 5 minutes and then MeI (3 μ L, 0.05 mmol) was added. After 15 minutes, the reaction was poured into water (10 mL) and extracted with EtOAc (25 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated.
- 10 The residue was purified by preparatory thin layer chromatography (5% MeOH/CH₂Cl₂) to afford 10.0 mg (83%) of Example **208**. R_f = 0.18 (5% MeOH/CH₂Cl₂). LCMS = 404; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.59 (bs, 2H), 7.44-7.47 (m, 3H), 7.21 (d, J = 4.0 Hz, 2H), 7.15 (t, J = 8.5 Hz, 2H), 6.11 (d, J = 1.5 Hz, 1H), 4.48 (s, 1H), 3.28 (s, 3H), 3.17 (d, J = 15 Hz, 1H), 2.75 (d, J = 15 Hz, 1H), 2.38
- 15 (m, 1H), 2.25 (d, J = 14.5 Hz, 1H), 1.68-1.79 (m, 2H), 1.48-1.57 (m, 2H), 1.18 (s, 3H), 1.10 (m, 1H).

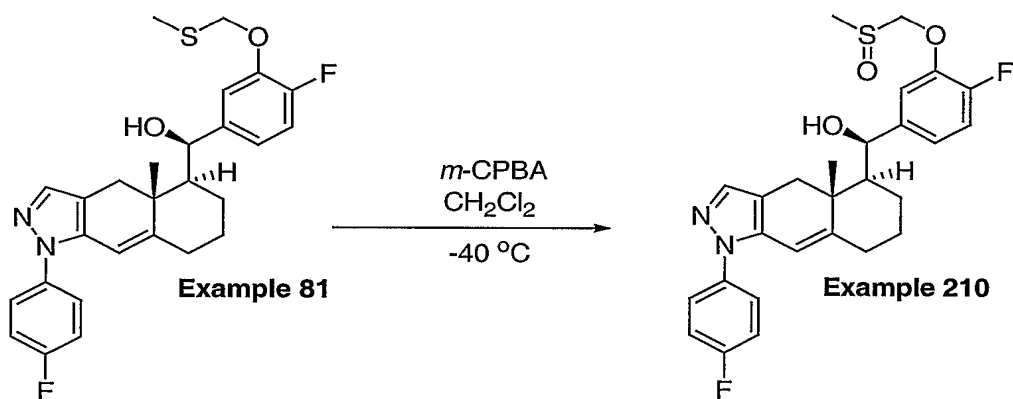
The following compound was synthesized starting from Example **32** and following a procedure analogous to that described for Examples **208**:

Compound	Molecular structure	LCMS (M+1) ⁺
209	<chem>CC1(C)C=C2C(=C1)C(=CN2C3=CC=CC=C3F)[C@@H](OC)[C@@H](C4=CC=CC=C4F)C5=CC=CC=C5</chem>	421

EXAMPLE 210

5

Step 1

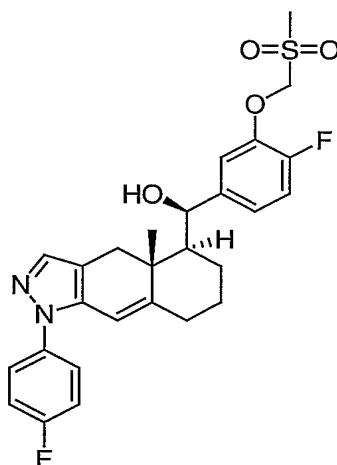


10

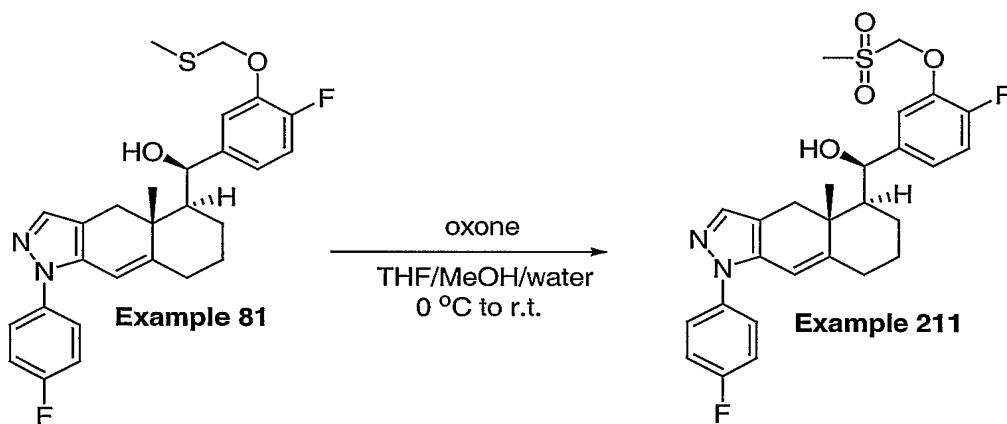
Example **81** (9.0 mg, 0.019 mmol) was dissolved in CH_2Cl_2 (1 mL) and the solution was cooled to -40°C . *m*-CPBA (6.4 mg, 0.037 mmol) was added and the reaction was stirred at -40°C for 20 minutes. The reaction was then diluted with EtOAc (25 mL), washed with saturated aq. NaHSO_3 , saturated NaHCO_3 , and brine (10 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (100% EtOAc to 5% MeOH/EtOAc) to afford 7.2 mg (78%) of Example **210**. $R_f = 0.19$ (EtOAc). LCMS = 499; $(\text{M}+1)^+$. ^1H NMR (CDCl_3 , 600 MHz) δ 7.43-7.46 (m, 3H), 7.26 (m, 1H), 7.14-

7.16 (m, 2H), 7.08 (dd, $J = 8.4, 10.0$ Hz, 1H), 6.97 (m, 1H), 6.11 (d, $J = 2.4$ Hz, 1H), 5.12 (s, 1H), 5.05 (dd, $J = 10.2, 3.0$ Hz, 1H), 4.97 (dd, $J = 10.2, 8.4$ Hz, 1H), 3.16 (d, $J = 15$ Hz, 1H), 2.73 (d, $J = 15$ Hz, 1H), 2.72 (s, 3H), 2.26-2.42 (m, 2H), 1.64-1.83 (m, 3H), 1.51 (m, 1H), 1.24 (s, 3H), 1.18 (m, 1H).

5

EXAMPLE 211

10 Step 1

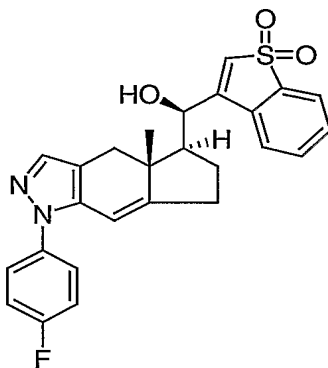


Example **81** (6.0 mg, 0.012 mmol) was dissolved in THF (100 μL) and MeOH (400 μL) was added. The solution was cooled to 0 $^\circ\text{C}$. Oxone (14 mg, 0.024 mmol) was dissolved in H_2O (400 μL) and this solution was added to the solution of **81**. The reaction was warmed to room temperature and stirred for 4 hours. The

reaction was then diluted with EtOAc (25 mL) and washed with water, saturated aq. NaHSO₃, saturated NaHCO₃, and brine (10 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparatory thin layer chromatography (60% EtOAc/hexanes) to afford 1.6 mg (25%) of Example **211**.

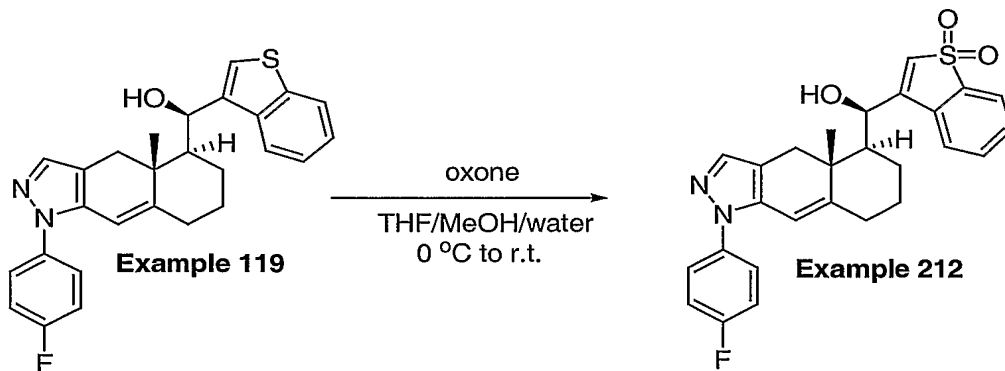
5 $R_f = 0.54$ (75%EtOAc/hexanes). LCMS = 515; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.45-7.48 (m, 3H), 7.01-7.26 (m, 4H), 7.02 (m, 1H), 6.12 (d, $J = 2.0$ Hz, 1H), 5.16 (s, 1H), 5.02 (s, 3H), 3.18 (d, $J = 15.5$ Hz, 1H), 3.07 (s, 3H), 2.74 (d, $J = 15$ Hz, 1H), 2.40 (m, 1H), 2.28 (m, 1H), 1.52-1.89 (m, 4H), 1.25 (s, 3H), 1.19 (m, 1H).

EXAMPLE 212



Step 1

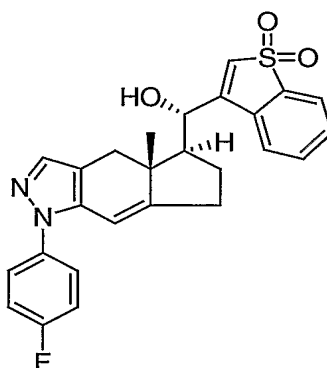
15



Example **119** (11.0 mg, 0.026 mmol) was dissolved in THF (200 μ L) and MeOH (200 μ L) was added. The solution was cooled to 0 °C. Oxone (32 mg, 0.051 mmol) was dissolved in H₂O (800 μ L) and this solution was added to the solution of **119**. The reaction was warmed to room temperature and stirred for 4

hours. At this point, additional oxone (32 mg, 0.051 mmol) was added as a solid. The reaction was stirred at room temperature for an additional 24 hours and then diluted with EtOAc (25 mL) and washed with water, saturated NaHCO₃, and brine (10 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparatory thin layer chromatography (60% EtOAc/hexanes) to afford 2.5 mg (21%) of Example **212**. $R_f = 0.13$ (40%EtOAc/hexanes). LCMS = 463; (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.76 (d, $J = 7.5$ Hz, 1H), 7.52-7.60 (m, 3H), 7.40-7.45 (m, 3H), 7.14 (t, $J = 8.5$ Hz, 2H), 6.72 (s, 1H), 6.14 (s, 1H), 5.02 (d, $J = 2.0$ Hz, 1H), 2.89 (d, $J = 14.5$ Hz, 1H), 2.65 (m, 1H), 2.55 (d, $J = 15$ Hz, 1H), 2.37-2.45 (m, 2H), 2.28 (m, 1H), 1.96-2.14 (m, 3H), 1.14 (s, 3H).

EXAMPLE 213



Example **213** was prepared in the same manner as example **212**, starting from example **120**.

BIOLOGICAL ASSAYS

The activity of the compounds of the present invention as modulators of the glucocorticoid receptor can be evaluated using the following assays:

Ligand Binding Assays

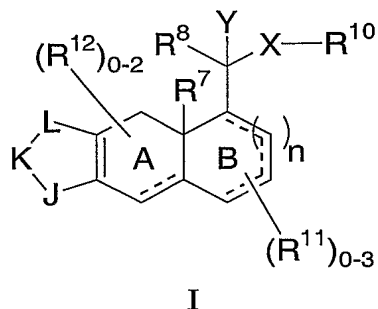
For the hGR α ligand binding assay, cytosols were prepared from recombinant baculovirus expressed receptors. Frozen cell pellets were dounce homogenized in ice cold KPO₄ buffer (10mM KPO₄, 20mM sodium molybdate, 1mM EDTA, 5mM DTT and complete protease inhibitor tablets from Boehringer

Mannheim) with a "B" plunger. The homogenates were centrifuged at 35,000 x g for 1 h at 4°C in a JA-20 rotor. The IC₅₀s were determined by incubating the cytosols at a final concentration of 2.5nM [1,2,4,6,7-³H] Dexamethasone in the presence of increasing concentrations (10⁻¹¹ to 10⁻⁶) of cold dexamethasone or the ligands at 4°C for 24 h. Bound and free were separated by a gel filtration assay, (Geissler et al., personal communication). Half of the reaction was added to a gel filtration plate (MILLIPORE) containing sephadex G-25 beads that was previously equilibrated with KPO₄ buffer containing 1mg/ml BSA and centrifuged at 1000 x g for 5 min.. The reaction plate was centrifuged at 1000 x g for 5 min. and the reactions were collected in a second 96-well plate and scintillation cocktail was added and counted in (Wallac) double coincidence beta counter. The IC₅₀s were calculated using a 4-parameter fit program.

Compounds of the invention demonstrated an activity in the range of 0.1 nM to 1 μM in the assay procedure described above.

WHAT IS CLAIMED IS:

1. A compound represented by Formula I



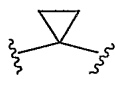
or a pharmaceutically acceptable salt or hydrate thereof, wherein:

10 n is 0, 1 or 2;

J is selected from NR^1 or $C(R^1)(R^2)$;

15 K is selected from NR^3 or $C(R^3)(R^4)$;

L is selected from NR^5 or $C(R^5)(R^6)$;

X is a bond, $-C(O)-$, $-N(R^{14})-$, $-N(R^{14})-C(O)-$, or  ;

20 R^1 , R^8 and R^{10} are each independently selected from the group consisting of:

- 25
- (1) C_{1-6} alkyl,
 - (2) C_{2-6} alkenyl,
 - (3) C_{3-6} alkynyl,
 - (4) C_{3-6} cycloalkyl,
 - (5) C_{1-6} alkoxy,
 - (6) C_{1-6} alkyl- $S(O)_k-$, wherein k is 0, 1 or 2,
 - (7) aryl,
 - (8) aralkyl,

- 5
- (9) HET,
 - (10) -C₁₋₆alkyl-HET,
 - (11) aryloxy,
 - (12) aroyloxy,
 - (13) aralkenyl,
 - (14) aralkynyl,
 - (15) hydrogen,
 - (16) hydroxy and
 - (17) C₁₋₆alkyl-N(R¹⁴)-S(O)_k-, wherein k is 0, 1 or 2,

10

wherein items (1) to (6) above and the alkyl portions of items (8), (10) and (17) above and the alkenyl portion of item (13) above and the alkynyl portion of item (14) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂, C₃₋₆cycloalkyl, C₁₋₆alkyl-S(O)_k- and aryl-S(O)_k-, wherein k is 0, 1 or 2, and

15

wherein items (7), (9), (11) and (12) above and aryl portion of items (8), (13) and (14) above and the HET portion of item (10) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

20

25

30

35

- (a) halo,
- (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl,
- (f) C₃₋₆alkynyl,
- (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (h) aryl,
- (i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
- (j) HET,
- (k) aralkyl,
- (l) aroyl,
- (m) aryloxy,
- (n) aralkoxy and

(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and
5 N(R¹⁴)₂, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo,
10 OR¹³ and C₁₋₄alkyl,

or when X is a bond then R⁸ and R¹⁰ may be joined together to form a 4- to 8-membered monocyclic ring, optionally containing 1-3 heteroatoms selected from O, S and NR¹⁴, and optionally containing 1 or 2 double bonds;

15

R², R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of:

- (1) hydrogen,
- (2) halo,
- 20 (3) C₁₋₆alkyl,
- (4) C₂₋₆alkenyl,
- (5) C₃₋₆alkynyl,
- (6) C₃₋₆cycloalkyl,
- (7) C₁₋₆alkoxy,
- 25 (8) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (9) aryl,
- (10) aralkyl,
- (11) HET and
- (12) -C₁₋₆alkyl-HET,

30 wherein items (3) to (8) above and the alkyl portions of items (10) and (12) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂ and C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2; and

wherein items (9) and (11) and the aryl portion of items (10) and the HET portion of item (12) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- 5 (a) halo,
 (b) OR¹³,
 (c) N(R¹⁴)₂,
 (d) C₁₋₆alkyl,
 (e) C₂₋₆alkenyl,
 10 (f) C₃₋₆alkynyl and
 (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,

wherein items (d) to (g) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂,

- 15 or R¹ and R³ or R³ and R⁵ may be joined together to form a double bond;

R⁷ is selected from the group consisting of:

- 20 (1) hydrogen,
 (2) OR¹³,
 (3) C₁₋₄alkyl,
 (4) aryl and
 (5) aralkyl,

- 25 wherein item (3) above and the alkyl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

- 30 wherein item (4) above and the aryl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
 (b) OR¹³,
 35 (c) N(R¹⁴)₂,

- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl and
- (f) C₃₋₆alkynyl,

wherein items (d) to (f) above are optionally substituted with from one up to the
 5 maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂;

Y is selected from the group consisting of:

- (1) hydrogen,
- 10 (2) -O-R⁹,
- (3) -S(O)_k-R⁹, wherein k is 0, 1 or 2,
- (4) -C-W-R⁹, wherein W is O or S(O)_k,
- (5) -N(R¹⁵)₂,
- (6) -S(O)_k-N(R¹⁵)₂,
- 15 (7) -N(R¹⁵)-S(O)_k-N(R¹⁵)₂,
- (8) NO₂,
- (9) -C(O)-R¹⁵,
- (10) -C(O)O-R¹⁵,
- (11) -CN,
- 20 (12) halo and
- (13) -O-S(O)_k-R¹⁵,

R⁹ is selected from the group consisting of: hydrogen, C₁₋₁₂alkyl and aryl, wherein C₁₋₁₂alkyl and aryl are optionally substituted from one up to the
 25 maximum number of substituents with halo, or when Y is OR⁹ then R⁸ and R⁹ may be joined together to form a carbonyl group;

each R¹¹ and R¹² is independently selected from the group consisting of:

- 30 (1) halo,
- (2) C₁₋₆alkyl,
- (3) C₂₋₆alkenyl,
- (4) C₁₋₆alkoxy and
- (5) hydroxy,

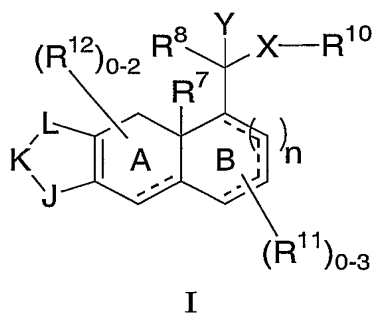
wherein items (2) to (4) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹², N(R¹³)₂ and C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2;

each R¹³ and R¹⁴ is independently selected from the group consisting of hydrogen, C₁₋₄alkyl and C₂₋₄alkenyl, each of said C₁₋₄alkyl and C₂₋₄alkenyl optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, C₁₋₄alkoxy, aryl, C₃₋₆cycloalkyl, CN and C₁₋₄alkyl-S(O)_k, wherein k is 0, 1 or 2;

each R¹⁵ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, aryl and C₁₋₁₂alkoxycarbonyl, wherein said C₁₋₆alkyl and C₁₋₁₂alkoxycarbonyl are optionally substituted from one up to the maximum number of substituable positions with halo and said aryl is optionally substituted from one up to the maximum number of substituable positions with halo and C₁₋₄alkyl, optionally substituted with 1-3 halo groups; and

HET is a 5- to 10-membered aromatic, partially aromatic or non-aromatic mono- or bicyclic ring, containing 1-4 heteroatoms selected from O, S and N, and optionally substituted with 1-2 oxo groups.

2. A compound according to Claim 1 represented by Formula I



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

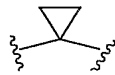
n is 0, 1 or 2;

J is selected from NR^1 or $\text{C}(\text{R}^1)(\text{R}^2)$;

5 K is selected from NR^3 or $\text{C}(\text{R}^3)(\text{R}^4)$;

L is selected from NR^5 or $\text{C}(\text{R}^5)(\text{R}^6)$;

10

X is a bond, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^{14})-$, $-\text{N}(\text{R}^{14})-\text{C}(\text{O})-$, or ;

R^1 , R^8 and R^{10} are each independently selected from the group consisting of:

- (1) C_{1-6} alkyl,
- (2) C_{2-6} alkenyl,
- 15 (3) C_{3-6} alkynyl,
- (4) C_{3-6} cycloalkyl,
- (5) C_{1-6} alkoxy,
- (6) C_{1-6} alkyl- $\text{S}(\text{O})_k-$, wherein k is 0, 1 or 2,
- (7) aryl,
- 20 (8) aralkyl,
- (9) HET,
- (10) $-\text{C}_{1-6}$ alkyl-HET,
- (11) aryloxy,
- (12) aroyloxy,
- 25 (13) aralkenyl,
- (14) aralkynyl,
- (15) hydrogen,
- (16) hydroxy and
- (17) C_{1-6} alkyl- $\text{N}(\text{R}^{14})-\text{S}(\text{O})_k-$, wherein k is 0, 1 or 2,

30

wherein items (1) to (6) above and the alkyl portions of items (8), (10) and (17) above and the alkenyl portion of item (13) above and the alkynyl portion of item (14) above are optionally substituted from one up to the maximum number of substitutable

positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂, C₃₋₆cycloalkyl and C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2, and

wherein items (7), (9), (11) and (12) above and aryl portion of items (8), (13) and (14) above and the HET portion of item (10) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
- (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl,
- (f) C₃₋₆alkynyl,
- (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (h) aryl,
- (i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
- (j) HET,
- (k) aralkyl,
- (l) aroyl,
- (m) aryloxy,
- (n) aralkoxy and
- (o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and C₁₋₄alkyl,

or when X is a bond then R⁸ and R¹⁰ may be joined together to form a 4- to 8-membered monocyclic ring, optionally containing 1-3 heteroatoms selected from O, S and NR¹⁴, and optionally containing 1 or 2 double bonds;

R², R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of:

- (1) hydrogen,
- (2) halo,
- (3) C₁₋₆alkyl,
- (4) C₂₋₆alkenyl,
- (5) C₃₋₆alkynyl,
- (6) C₃₋₆cycloalkyl,
- (7) C₁₋₆alkoxy,
- (8) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (9) aryl,
- (10) aralkyl,
- (11) HET and
- (12) -C₁₋₆alkyl-HET,

wherein items (3) to (8) above and the alkyl portions of items (10) and (12) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂ and C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2; and

wherein items (9) and (11) and the aryl portion of items (10) and the HET portion of item (12) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
- (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl,
- (f) C₃₋₆alkynyl and
- (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,

wherein items (d) to (g) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂,

or R¹ and R³ or R³ and R⁵ may be joined together to form a double bond;

R⁷ is selected from the group consisting of:

- 5 (1) hydrogen,
 (2) OR¹³,
 (3) C₁₋₄alkyl,
 (4) aryl and
 (5) aralkyl,

10 wherein item (3) above and the alkyl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

15 wherein item (4) above and the aryl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
 (b) OR¹³,
20 (c) N(R¹⁴)₂,
 (d) C₁₋₆alkyl,
 (e) C₂₋₆alkenyl and
 (f) C₃₋₆alkynyl,

 wherein items (d) to (f) above are optionally substituted with from one up to the
25 maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂;

Y is selected from the group consisting of:

- 30 (1) hydrogen,
 (2) -O-R⁹,
 (3) -S(O)_k-R⁹, wherein k is 0, 1 or 2,
 (4) -C-W-R⁹, wherein W is O or S(O)_k,
 (5) -N(R¹⁵)₂,
 (6) -S(O)_k-N(R¹⁵)₂,

- 5
- (7) $-N(R^{15})-S(O)_k-N(R^{15})_2$,
 - (8) NO_2 ,
 - (9) $-C(O)-R^{15}$,
 - (10) $-C(O)O-R^{15}$,
 - (11) $-CN$,
 - (12) halo and
 - (13) $-O-S(O)_k-R^{15}$,

10 R^9 is selected from the group consisting of: hydrogen, C_{1-12} alkyl and aryl, wherein C_{1-12} alkyl and aryl are optionally substituted from one up to the maximum number of substituents with halo, or when Y is OR^9 then R^8 and R^9 may be joined together to form a carbonyl group;

15 each R^{11} and R^{12} is independently selected from the group consisting of:

- (1) halo,
- (2) C_{1-6} alkyl,
- (3) C_{2-6} alkenyl,
- (4) C_{1-6} alkoxy and
- 20 (5) hydroxy,

wherein items (2) to (4) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{12} , $N(R^{13})_2$ and C_{1-6} alkyl- $S(O)_k$ -, wherein k is 0, 1 or 25 2;

each R^{13} and R^{14} is independently selected from the group consisting of hydrogen and C_{1-4} alkyl, optionally substituted from one up to the maximum number of substitutable positions with halo; and

30 each R^{15} is independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, aryl and C_{1-12} alkoxycarbonyl, wherein said C_{1-6} alkyl and C_{1-12} alkoxycarbonyl are optionally substituted from one up to the maximum number of substitutable positions with halo and said aryl is optionally substituted from one up to

the maximum number of substituable positions with halo and C₁₋₄alkyl, optionally substituted with 1-3 halo groups.

5 3. The compound according to Claim 2 wherein:

J is NR1;

K is NR³;

L is $C(\mathbb{R}^5)(\mathbb{R}^6)$; and

R³ and R⁵ are joined together to form a double bond.

4. The compound according to Claim 2 wherein the optional double bond shown in ring A of the compound of Formula I is present.

5. The compound according to Claim 2 wherein R¹ is aryl or
20 HET, said aryl or HET optionally substituted from one up to the maximum number of
substitutable positions with a substituent independently selected from the group
consisting of:

- 25 (a) halo,
(b) OR¹³,
(c) N(R¹⁴)₂,
(d) C₁₋₆alkyl,
(e) C₂₋₆alkenyl,
(f) C₃₋₆alkynyl,
(g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
30 (h) aryl,
(i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
(j) HET,
(k) aralkyl,
(l) aroyl,

- (m) aryloxy,
- (n) aralkoxy and
- (o) CN,

5 wherein items (d) to (g) above and the alkyl portions of item (k) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

10 wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and C₁₋₄alkyl.

15 6. The compound according to Claim 5 wherein R¹ is phenyl, optionally substituted with 1-3 halo groups.

7. The compound according to Claim 2 wherein Y is OR⁹.

20 8. The compound according to Claim 7 wherein R⁹ is hydrogen.

9. The compound according to Claim 2 wherein R⁷ is methyl.

25 10. The compound according to Claim 2 wherein R⁸ is hydrogen or methyl.

11. The compound according to Claim 2 wherein X is a bond.

30 12. The compound according to Claim 2 wherein R¹⁰ is selected from the group consisting of:

- (1) C₁₋₆alkyl,
- (2) C₂₋₆alkenyl,
- (3) C₃₋₆alkynyl,
- (4) C₃₋₆cycloalkyl,
- 35 (5) C₁₋₆alkoxy,

(6) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,

wherein items (1) to (6) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³, N(R¹⁴)₂, C₃₋₆cycloalkyl and C₁₋₆alkyl-S(O)_k,

5 wherein k is 0, 1 or 2.

13. The compound according to Claim 2 wherein R¹⁰ is selected from the group consisting of:

- (1) phenyl
- 10 (2) naphthyl,
- (3) benzyl,
- (4) phenethyl,
- (5) phenoxy,
- (6) benzoyl and
- 15 (7) benzoyloxy,

wherein the aryl portions of items (1) to (7) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

- (a) halo,
- 20 (b) OR¹³,
- (c) N(R¹⁴)₂,
- (d) C₁₋₆alkyl,
- (e) C₂₋₆alkenyl,
- (f) C₃₋₆alkynyl,
- 25 (g) C₁₋₆alkyl-S(O)_k-, wherein k is 0, 1 or 2,
- (h) aryl,
- (i) aryl-S(O)_k-, wherein k is 0, 1 or 2,
- (j) HET,
- (k) aralkyl,
- 30 (l) aroyl,
- (m) aryloxy,
- (n) aralkoxy and
- (o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and N(R¹⁴)₂, and

5

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR¹³ and C₁₋₄alkyl.

10

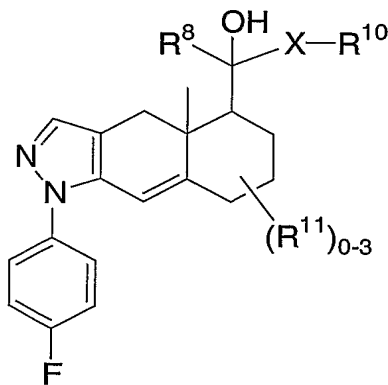
14. The compound according to Claim 2 wherein R¹⁰ is HET or -C₁₋₄alkyl-HET wherein HET is selected from the group consisting of:

- (1) pyridine,
- (2) thiophene and
- (3) furan,

15

or benzofused analogs of (1) to (3) above.

15. A compound according to Claim 1 of Formula II:



20

II

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is a bond;

25

R⁸ and R¹⁰ are each independently selected from the group consisting of:

- 5 (1) C₁₋₆alkyl, optionally substituted with hydroxy,
(2) C₂₋₆alkenyl,
(3) C₃₋₆alkynyl,
(4) C₃₋₆cycloalkyl,
(5) phenyl
(6) naphthyl,
(7) benzyl,
(8) phenethyl and
(9) pyridine, thiophene or furan, or benzofused analogs thereof,

10

and R⁸ is additionally selected from hydrogen,

wherein items (5), (6) and (9) above and aryl portion of items (7) and (8) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

15

- (a) halo,
(b) hydroxy,
(c) methoxy,
(d) C₁₋₄alkyl,
(e) trifluoromethyl,
(f) phenoxy,
(g) benzyloxy, optionally substituted with methoxy, and
(h) CN;

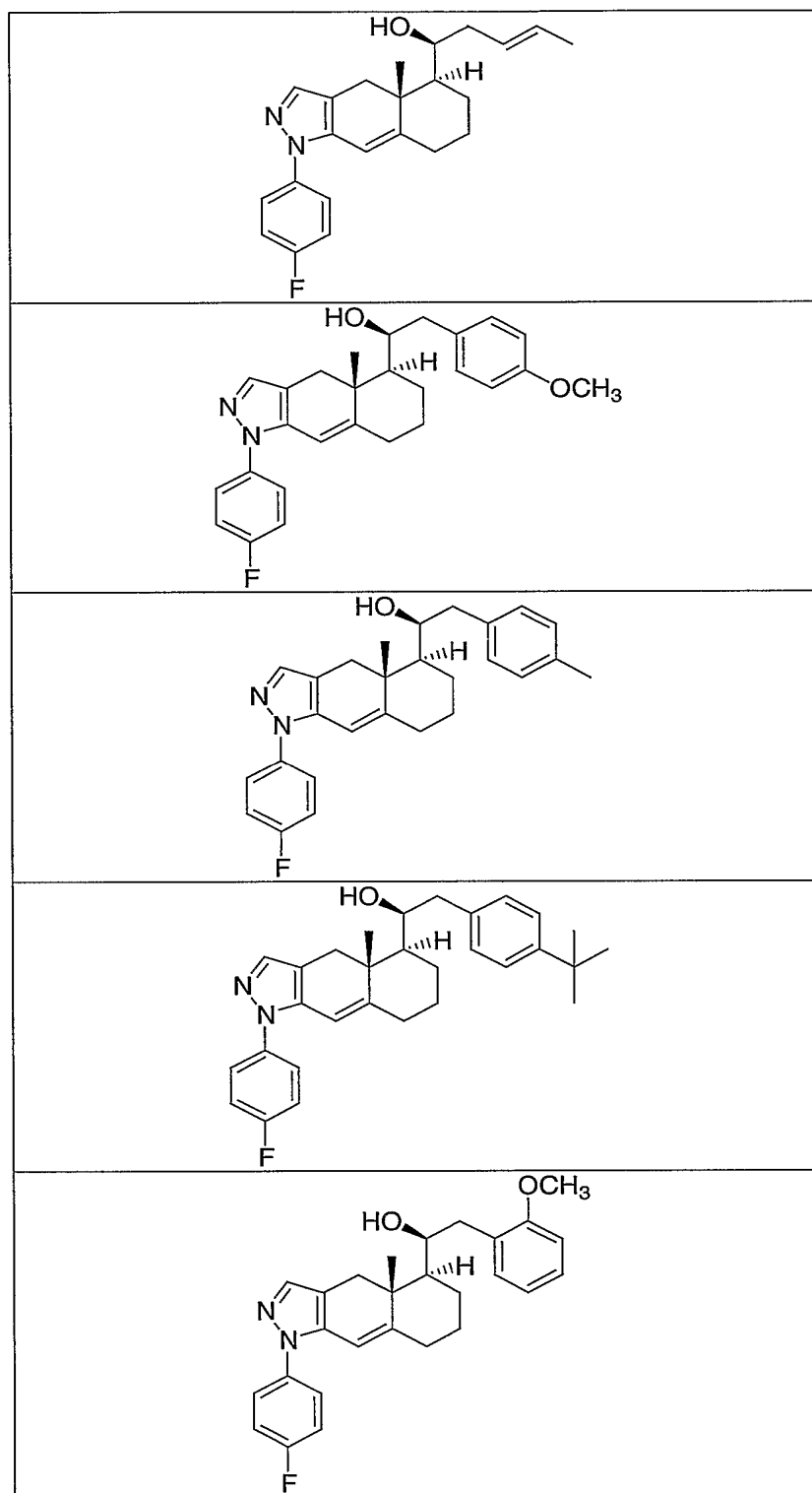
20

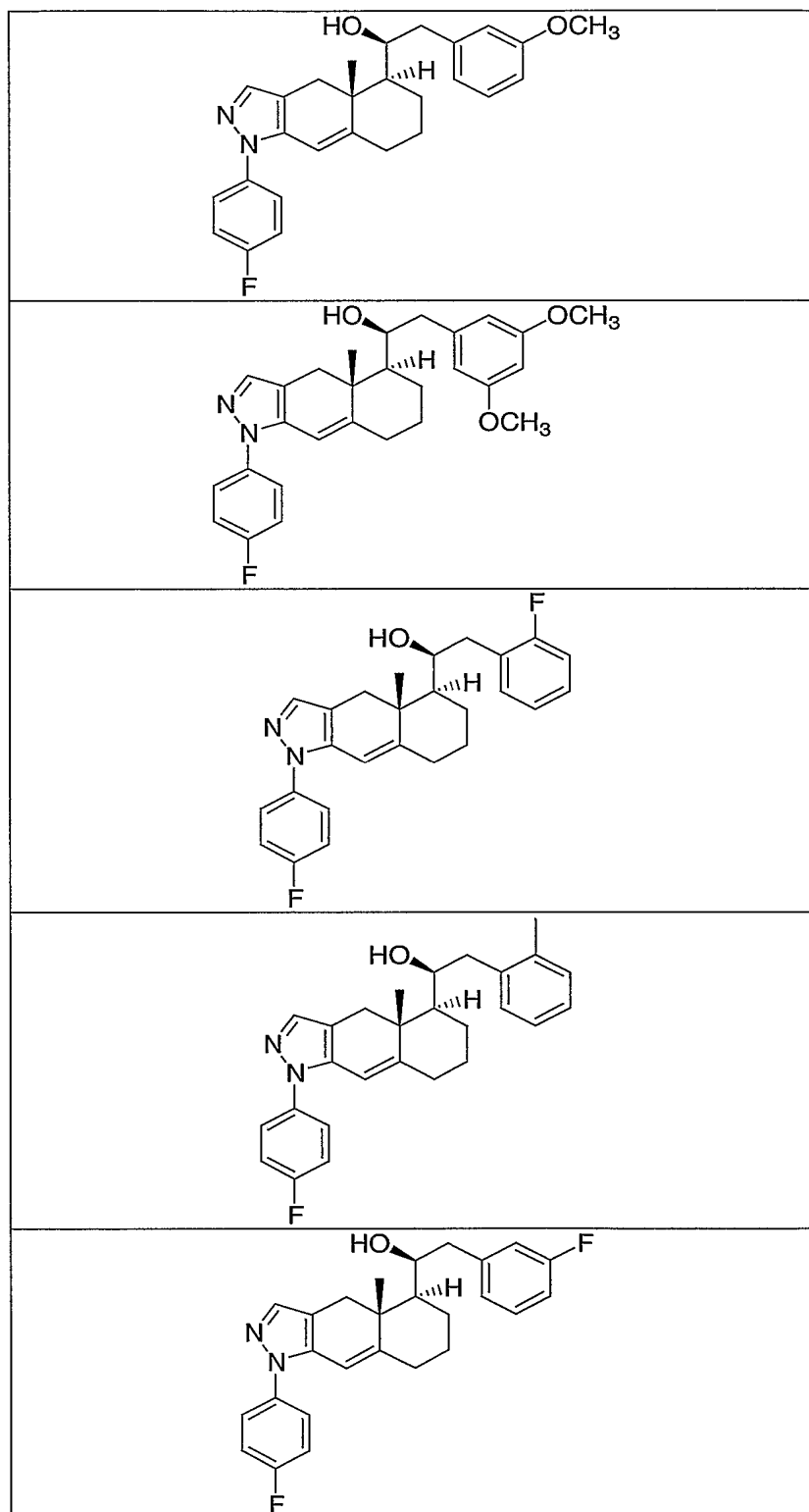
25 each R¹¹ is independently selected from the group consisting of:

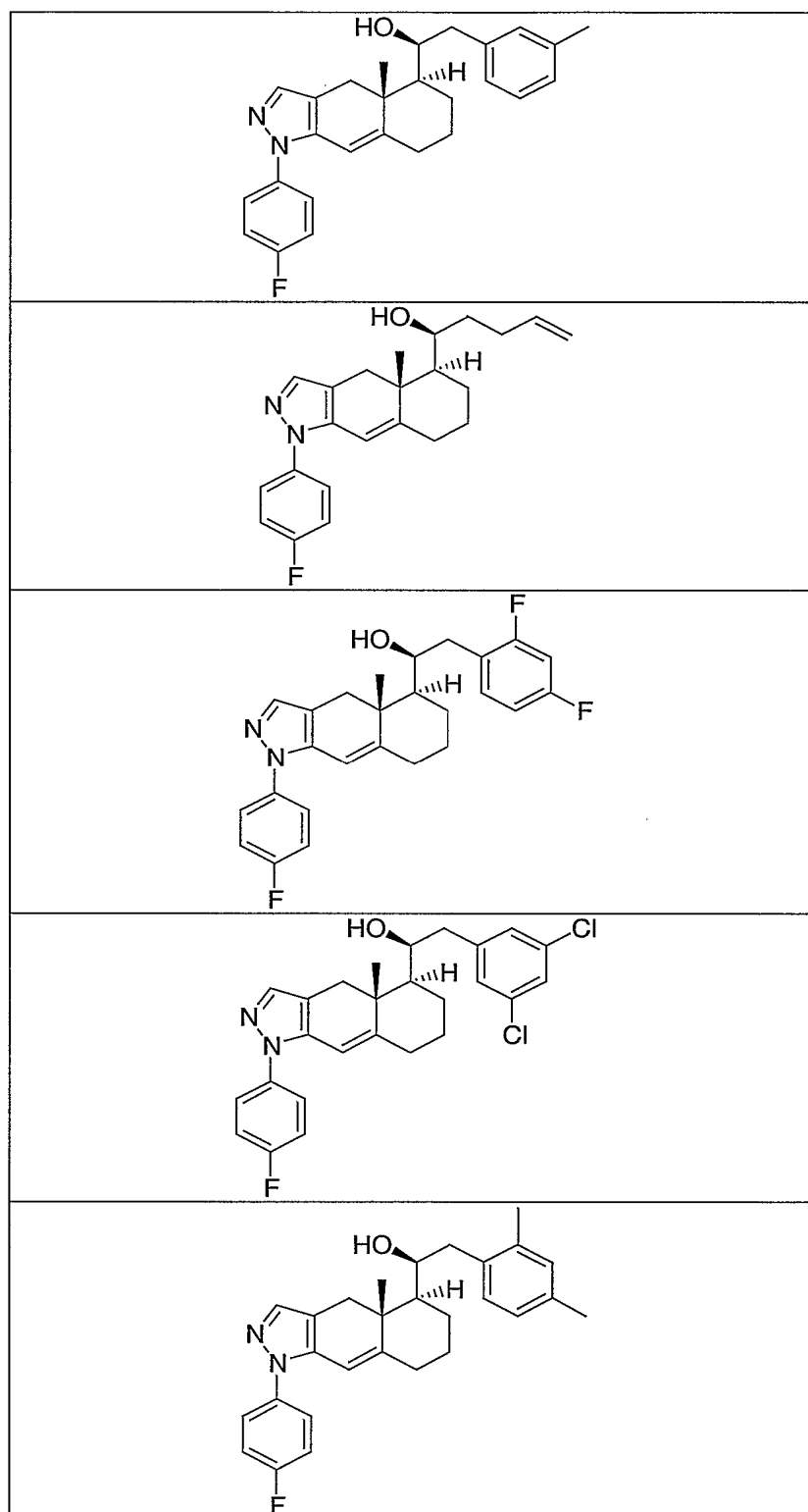
- (1) halo,
(2) methyl and
(3) hydroxy; and

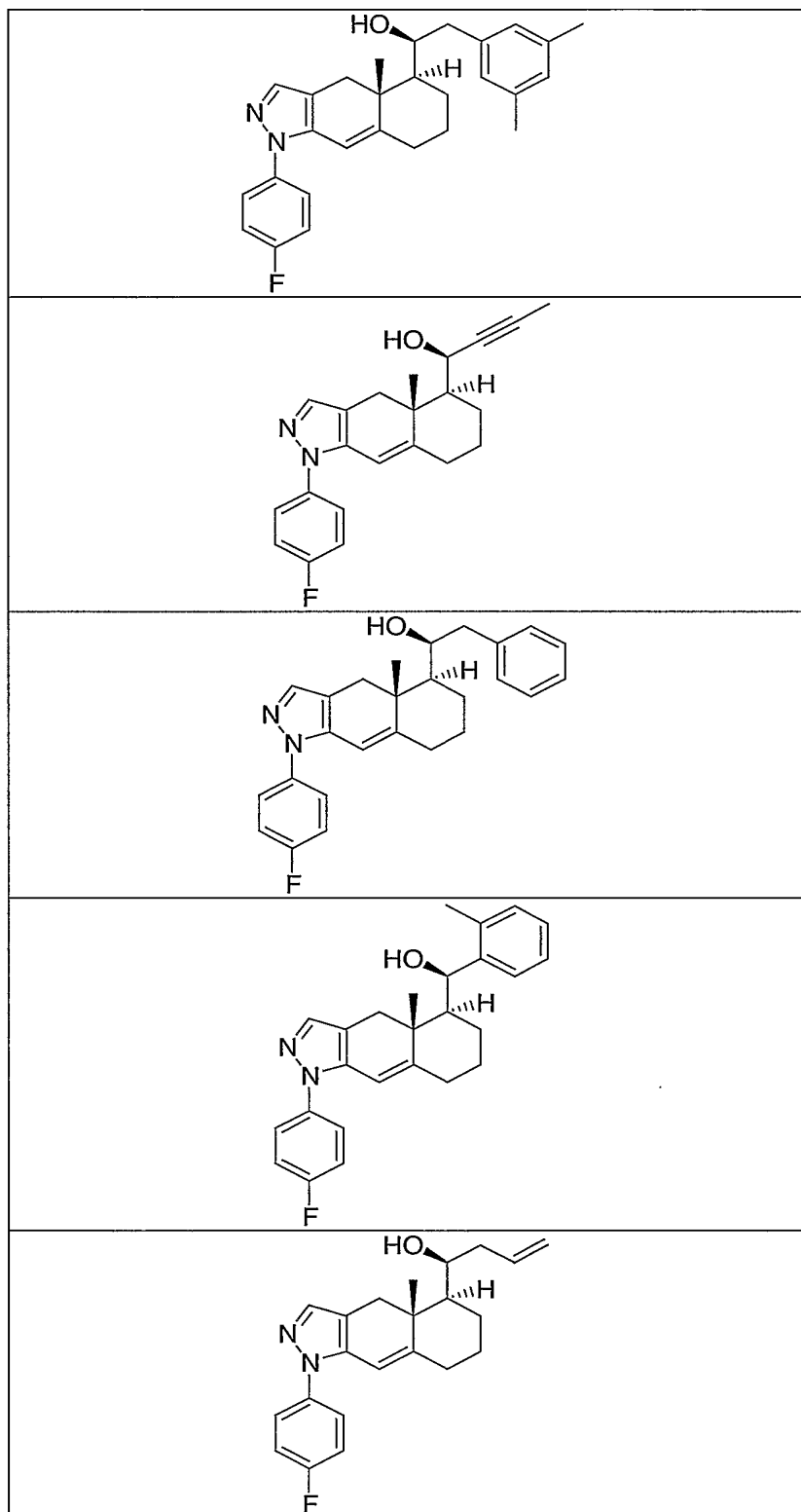
30 R¹⁴ is independently selected from the group consisting of hydrogen and C₁₋₄alkyl.

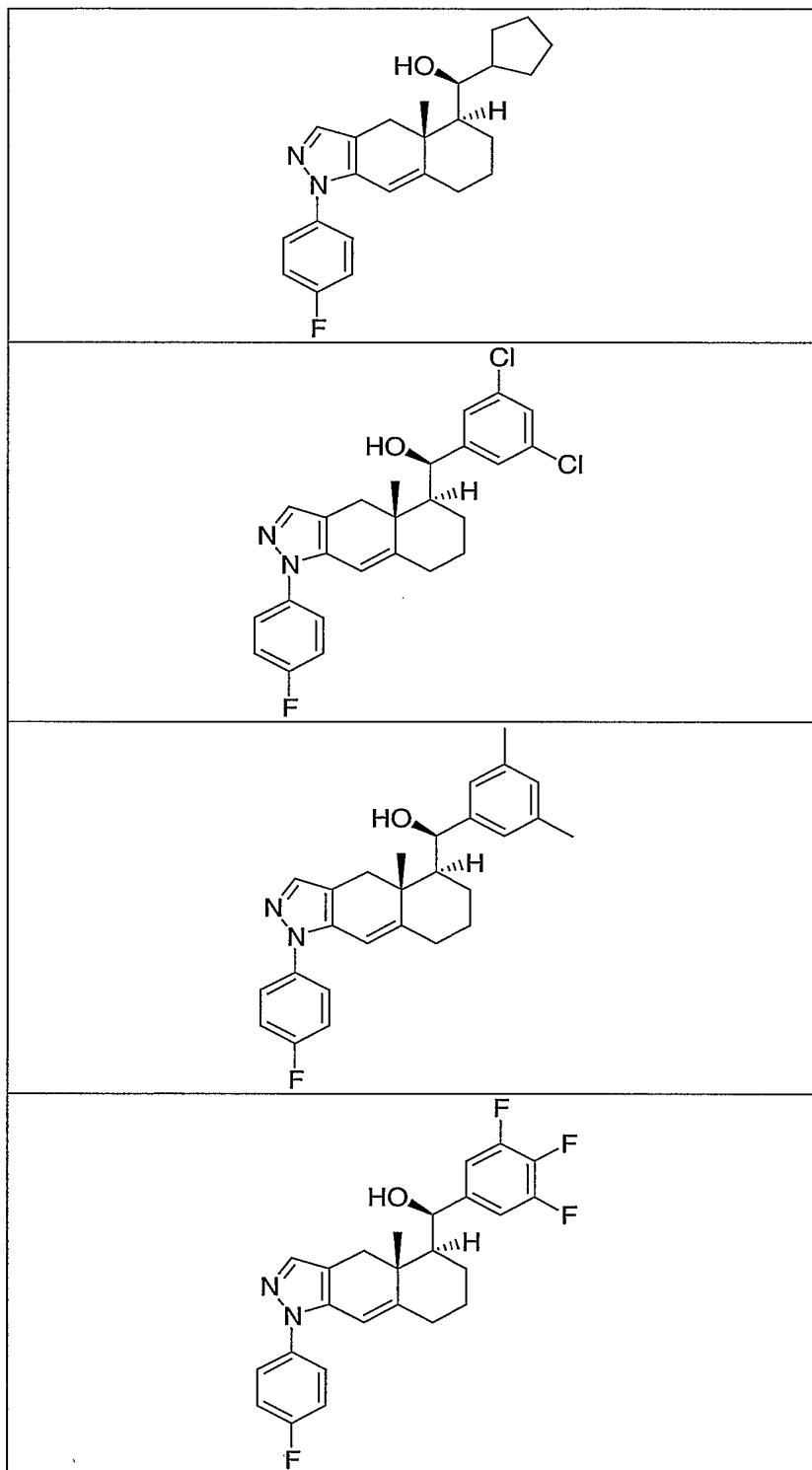
16. The compound according to Claim 15 wherein R⁸ is selected from the group consisting of hydrogen and C₁₋₄alkyl.

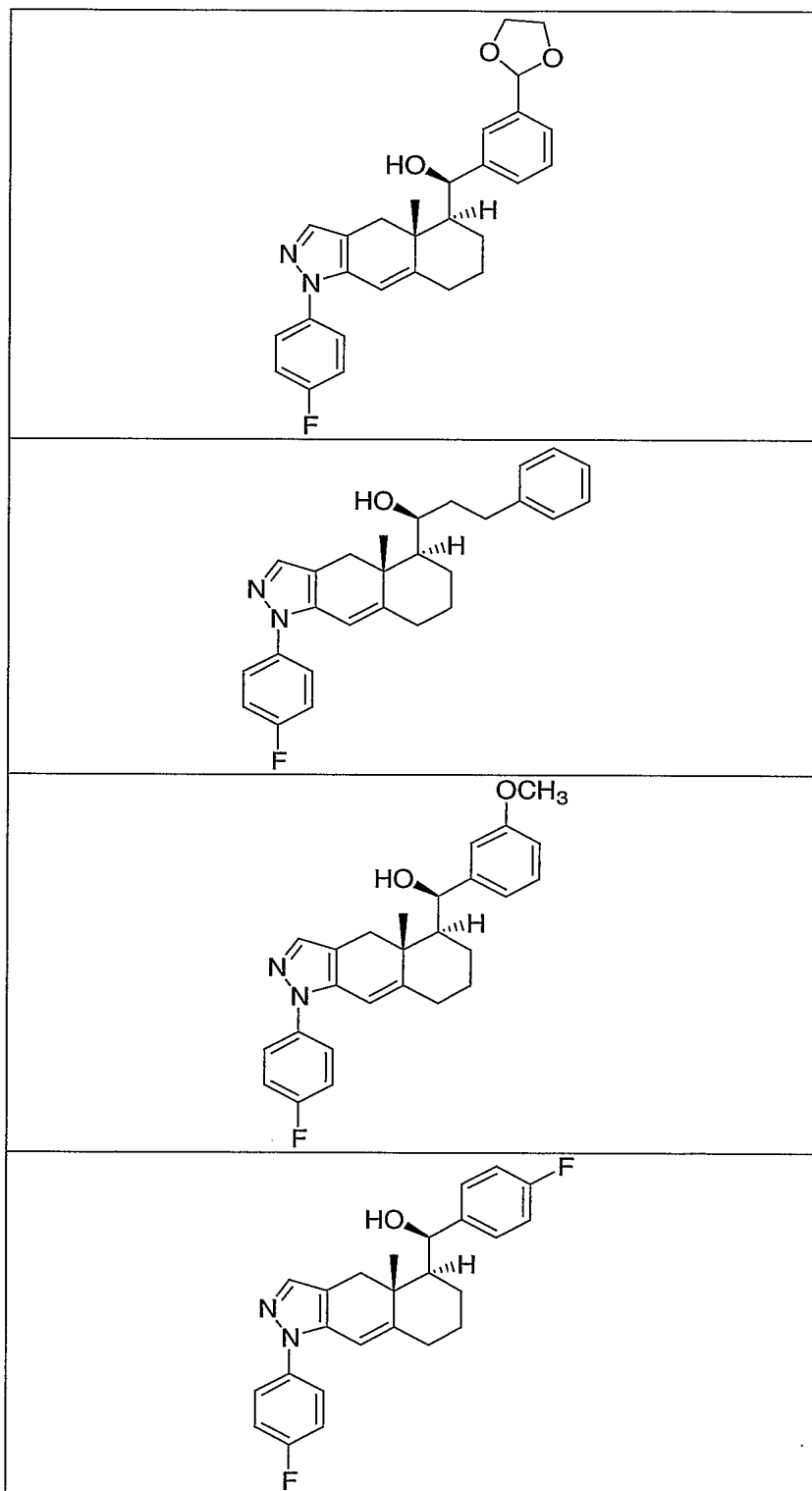


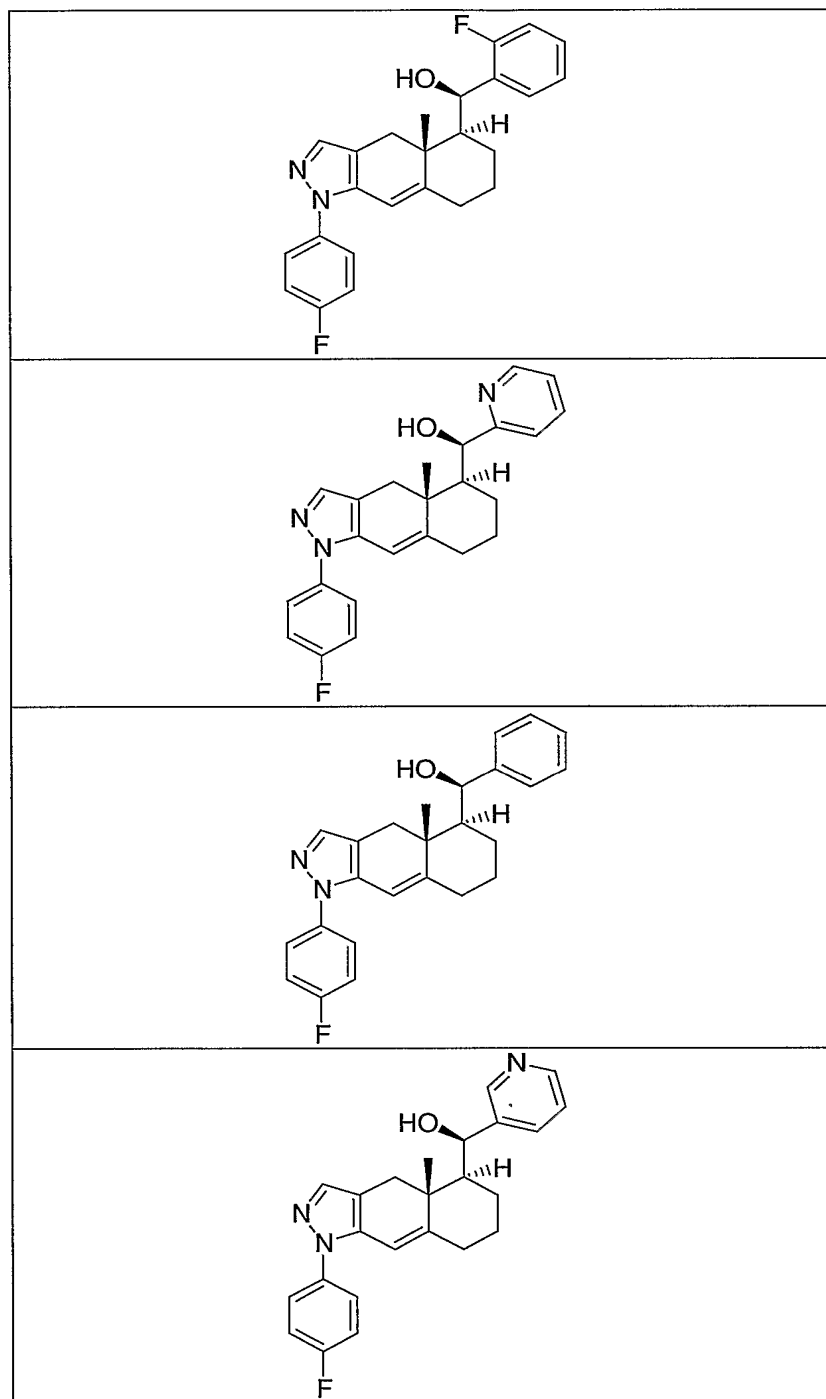


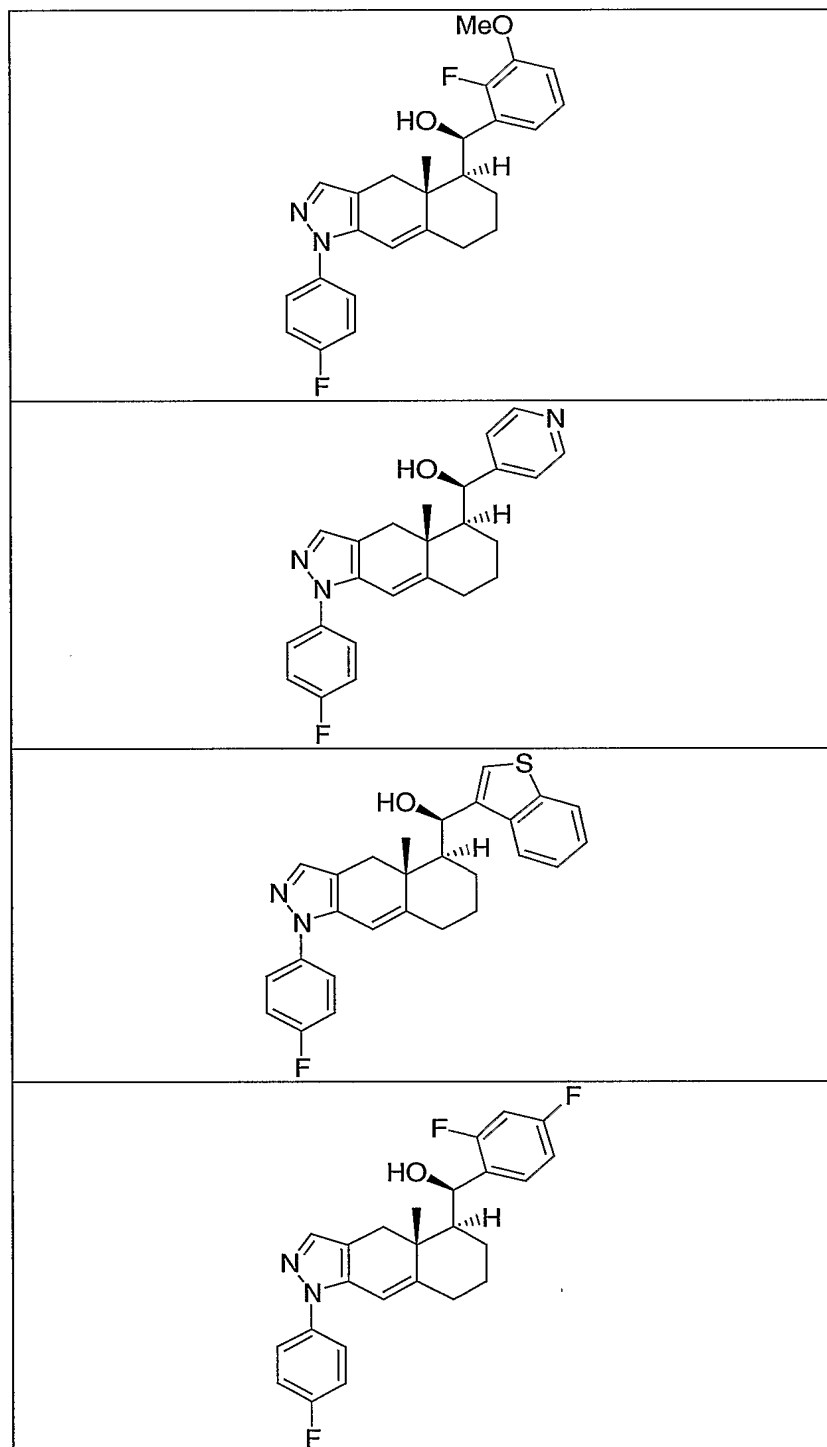


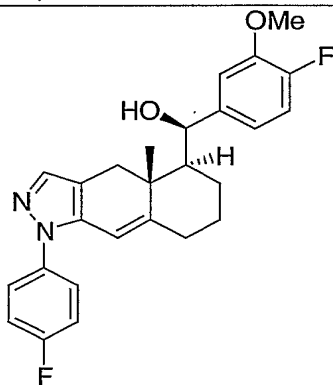
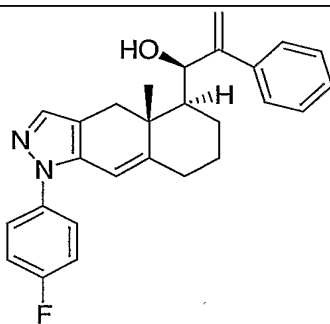
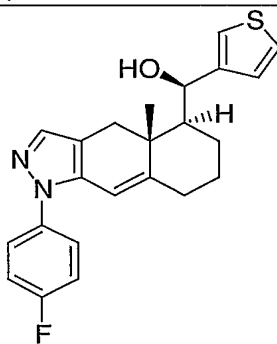
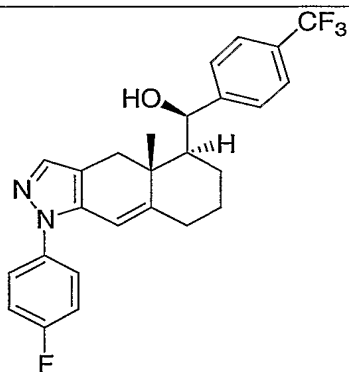


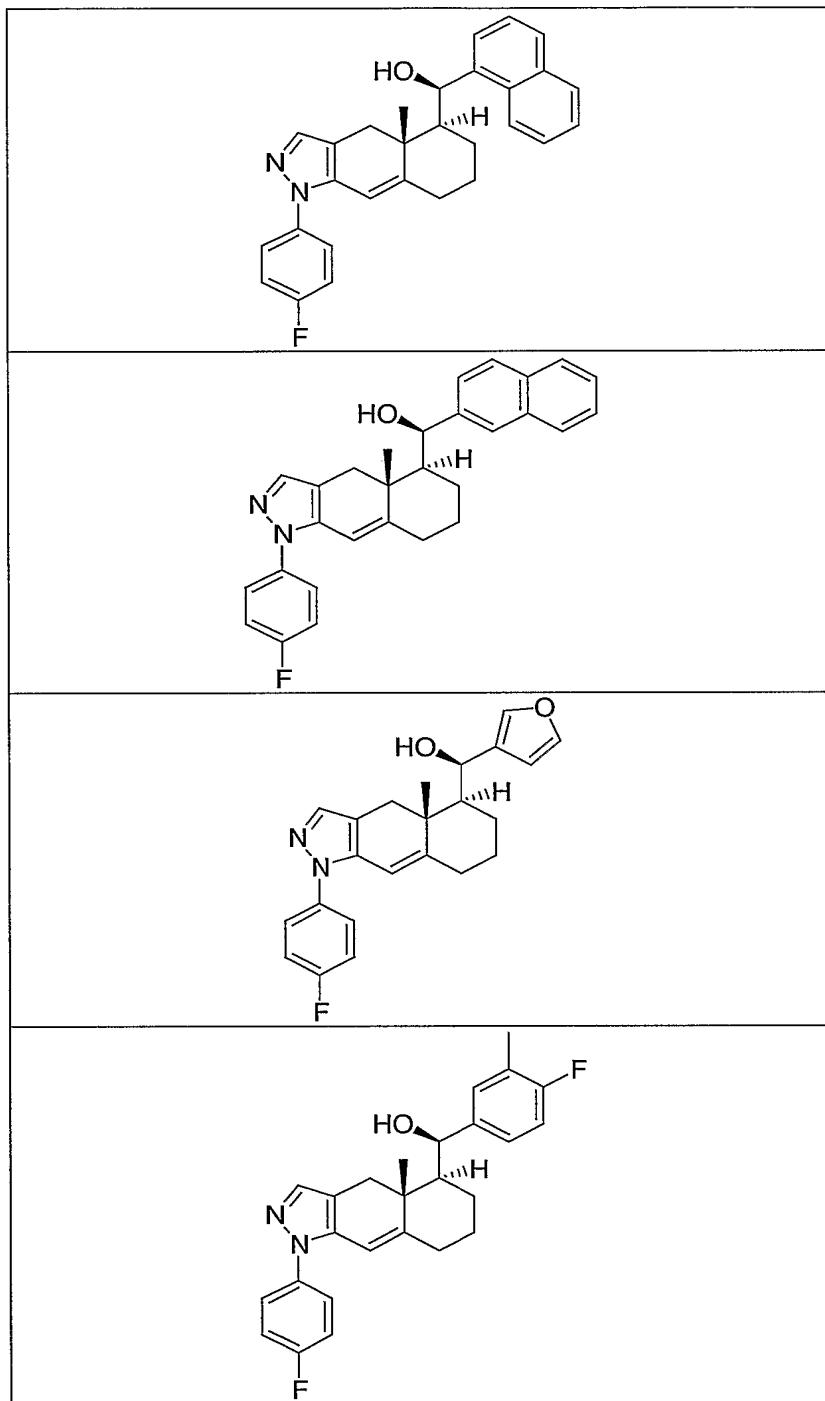


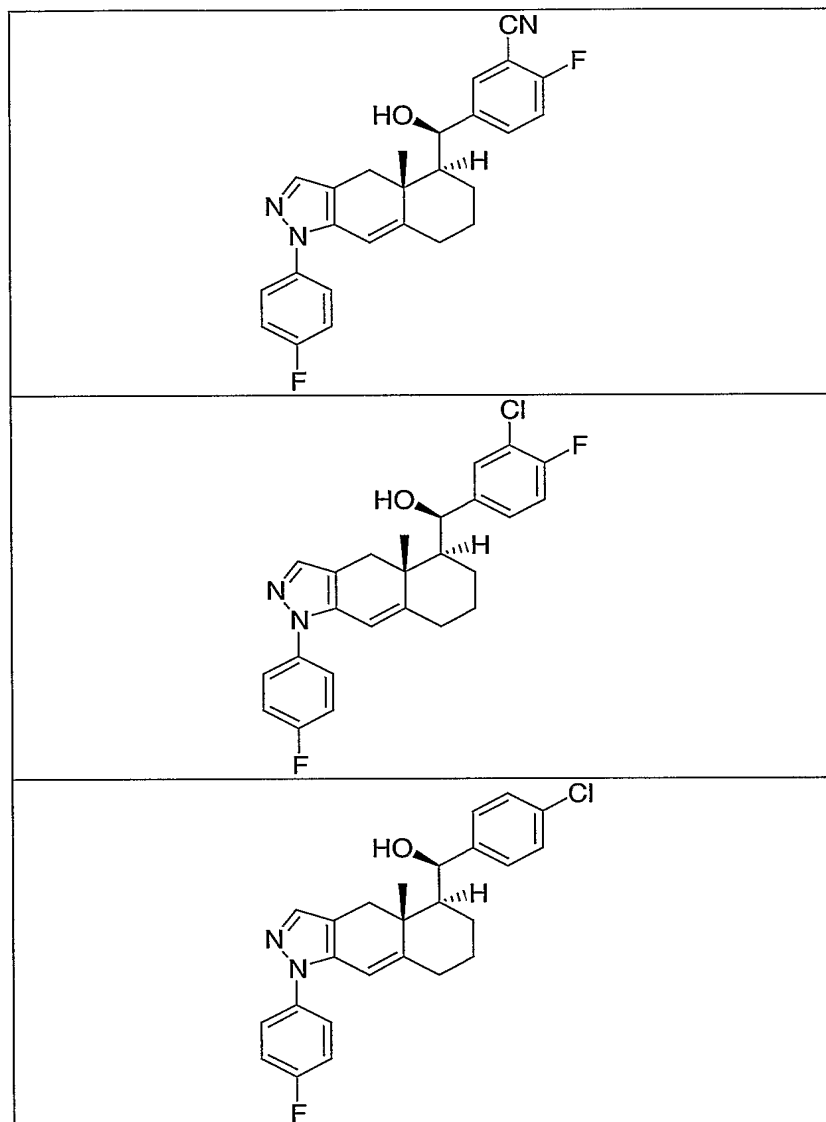


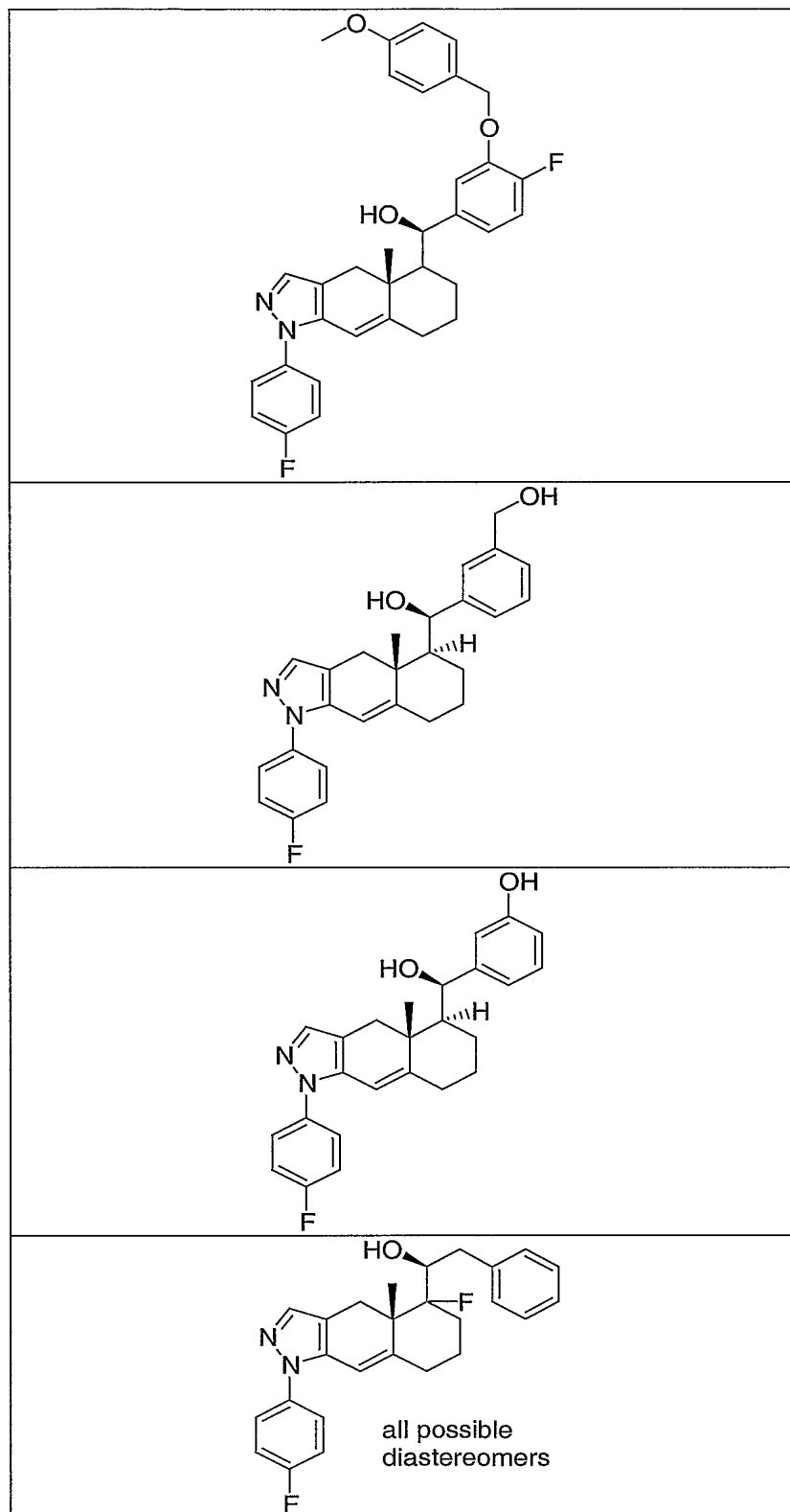


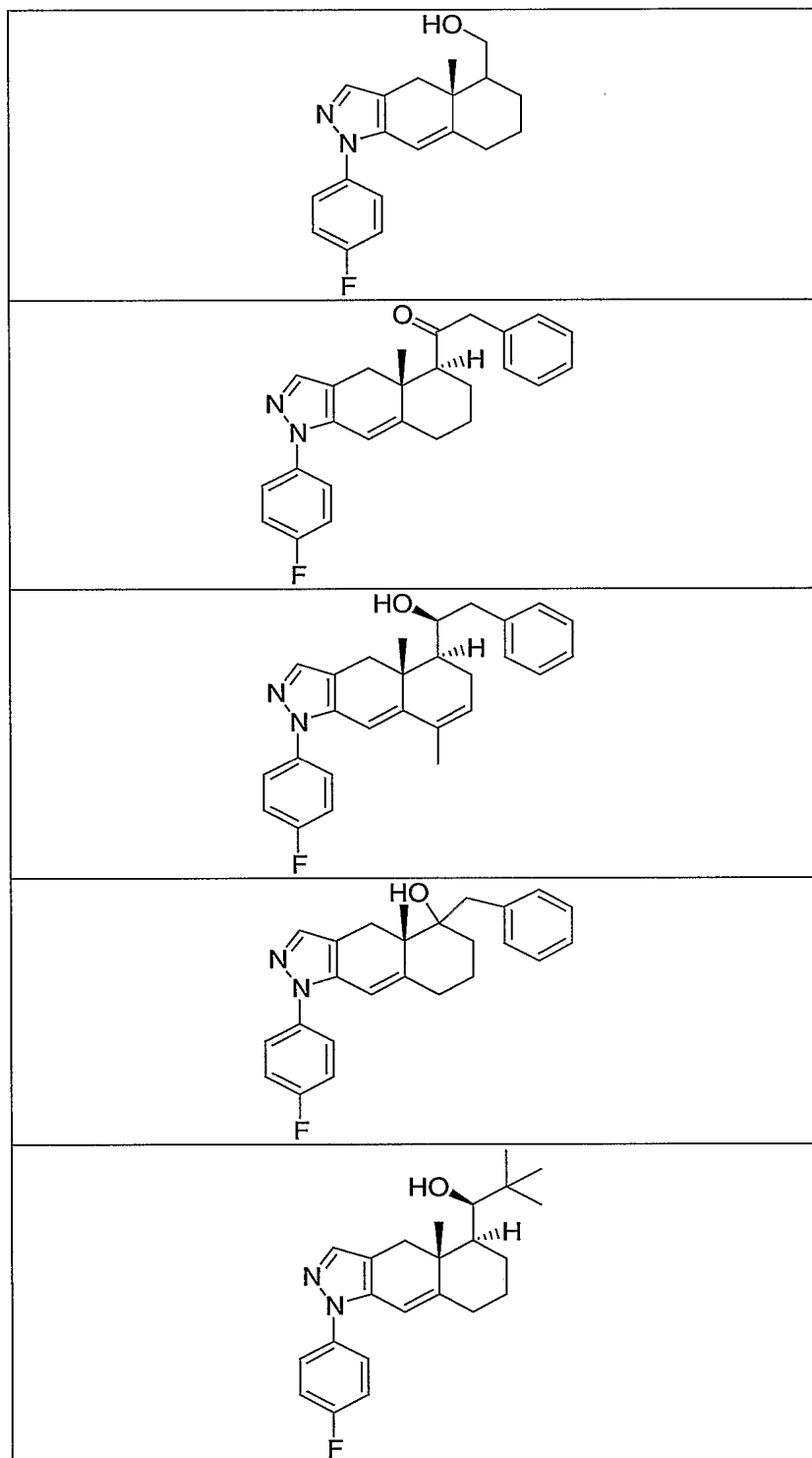


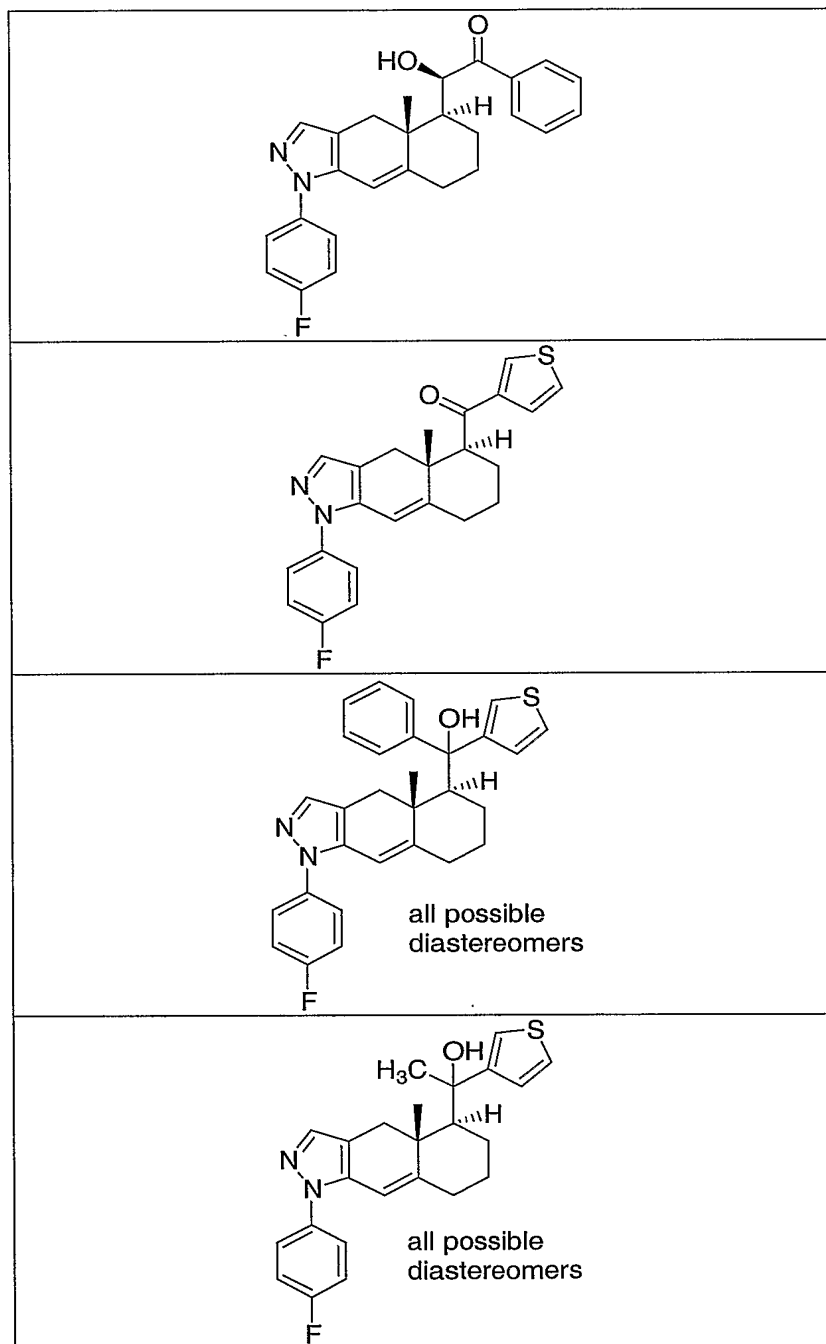


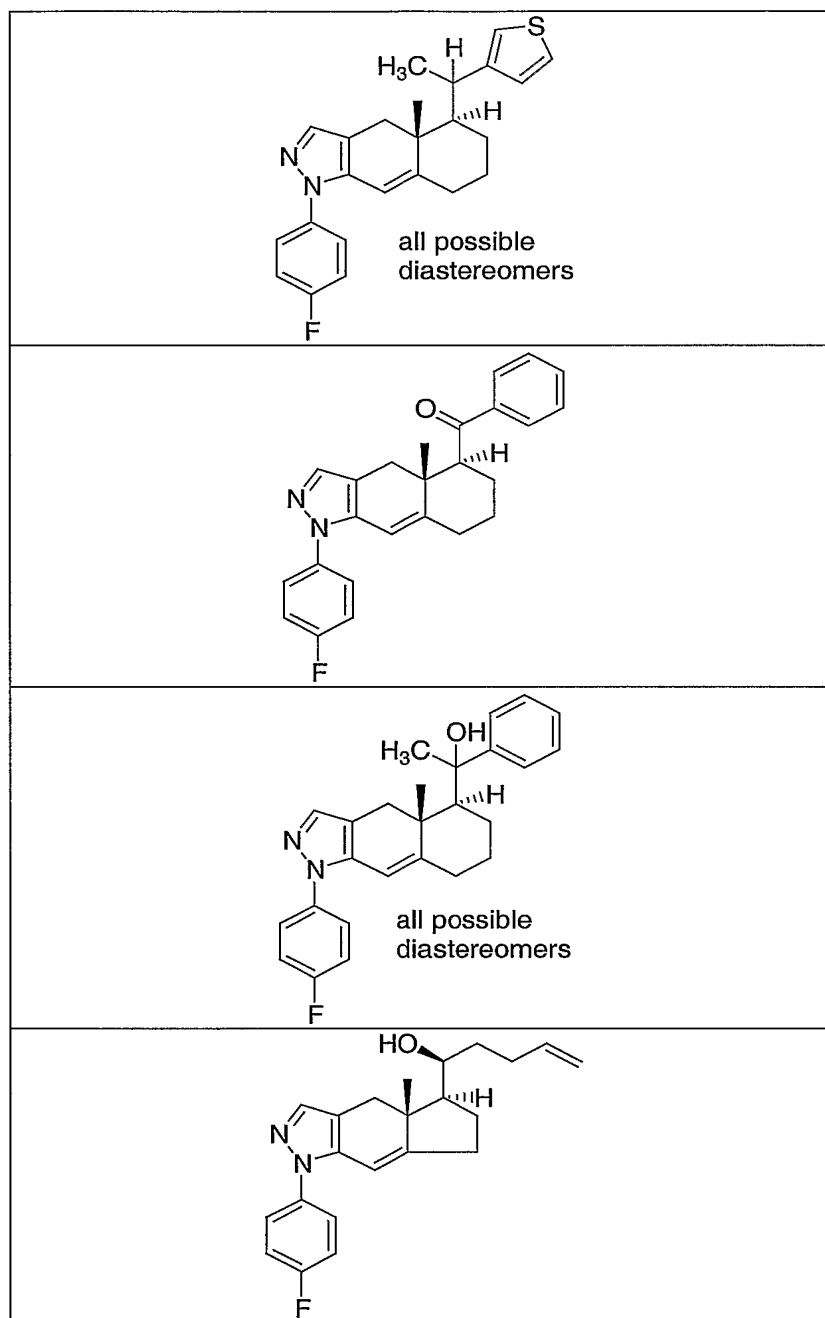


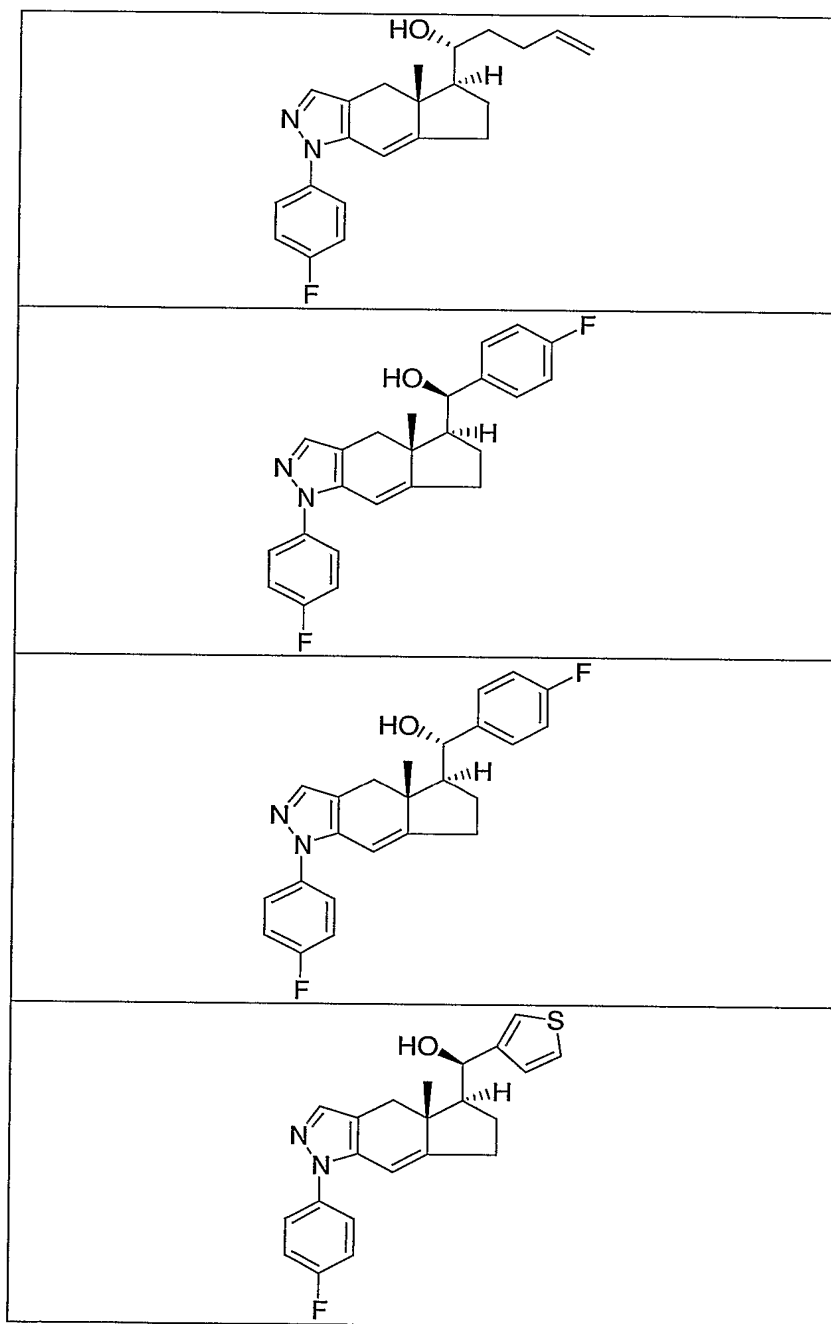


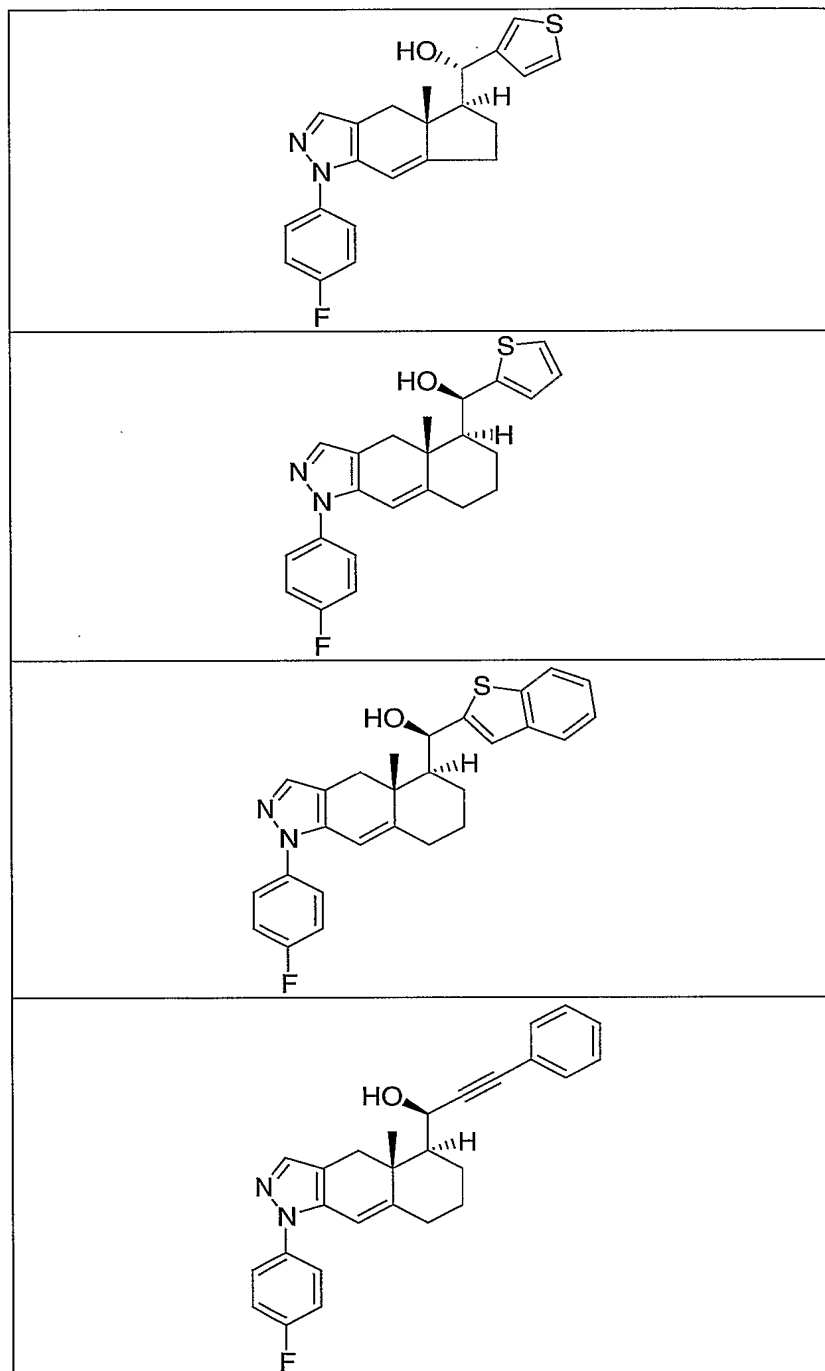


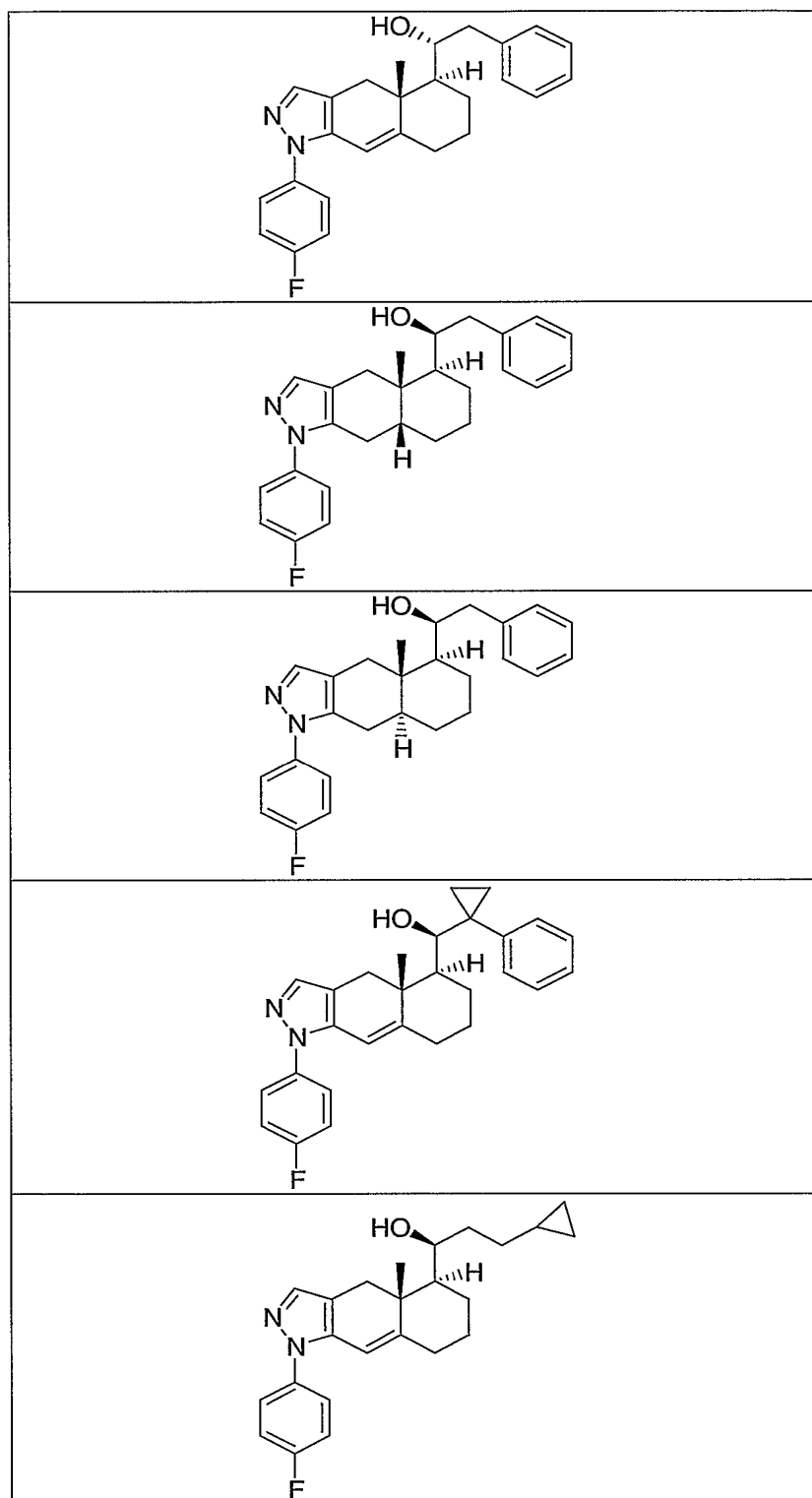


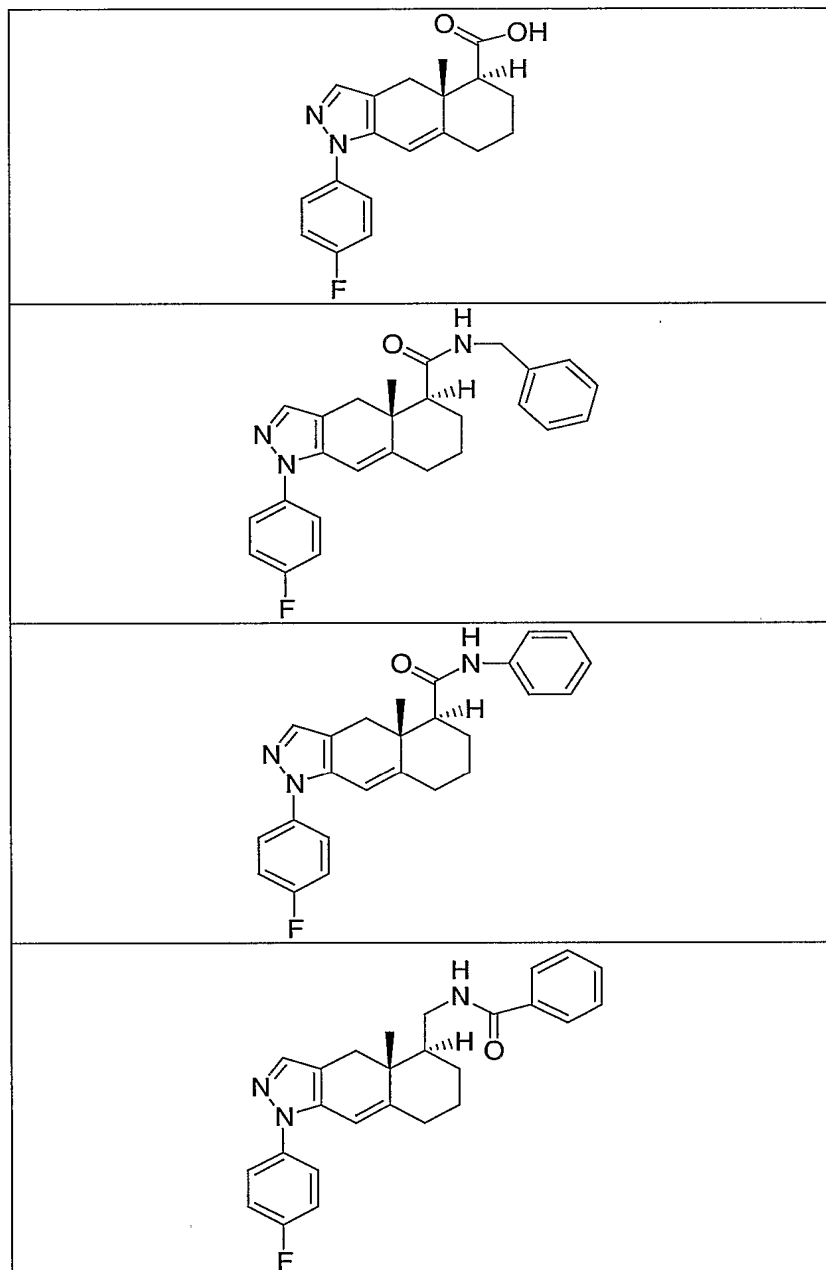


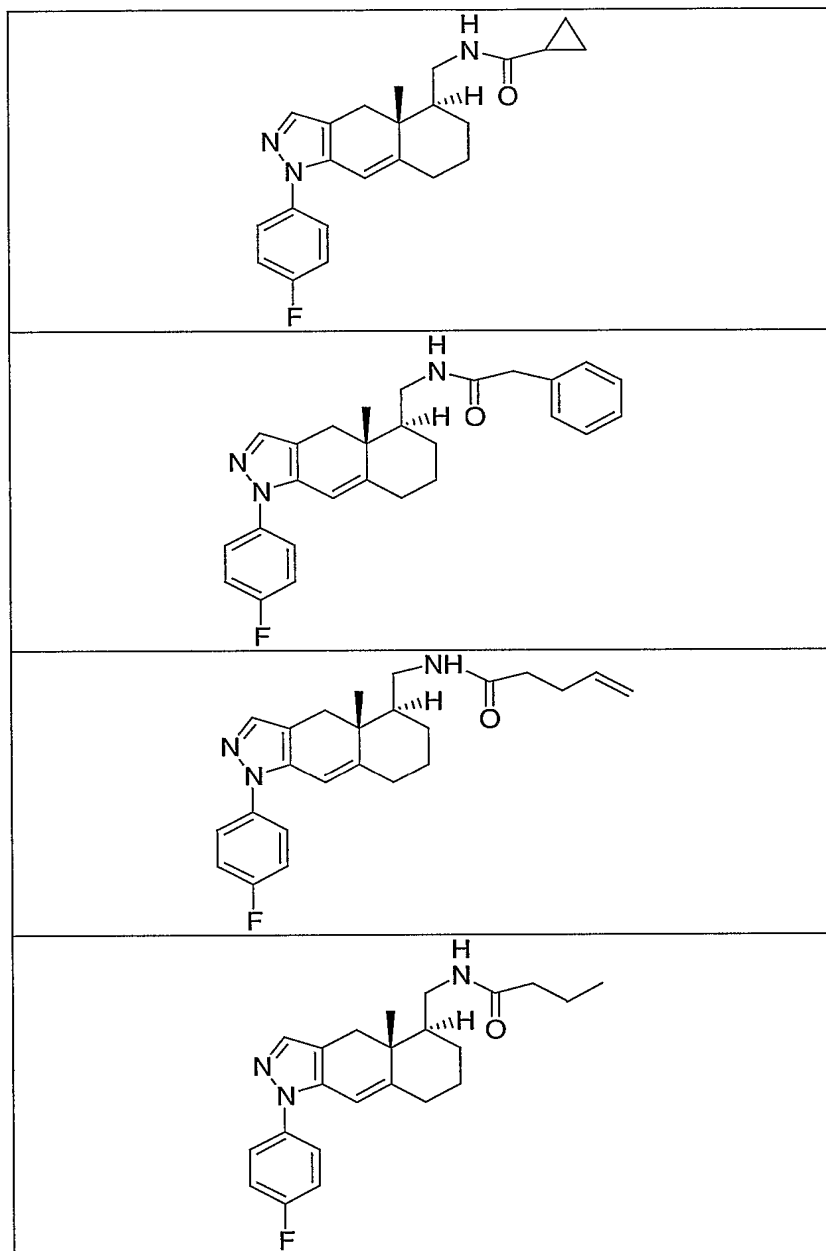


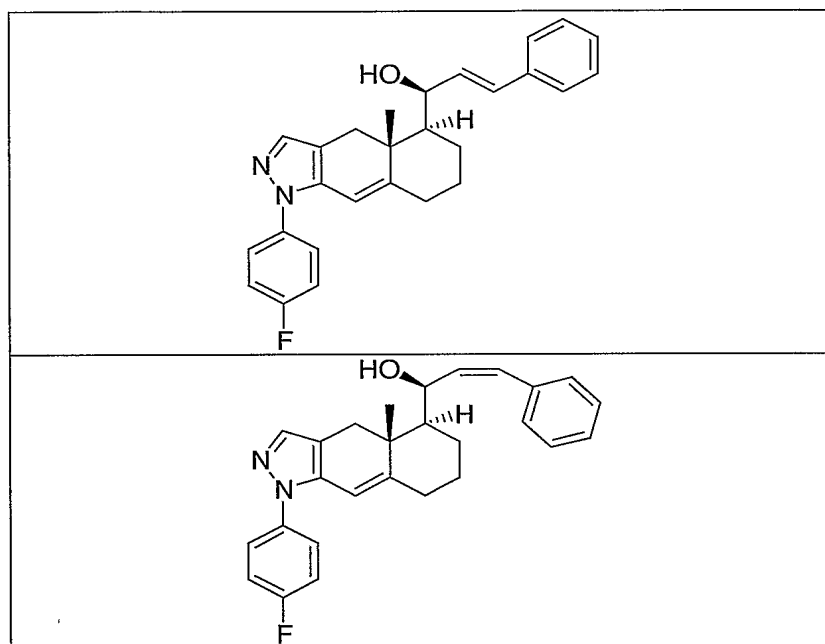






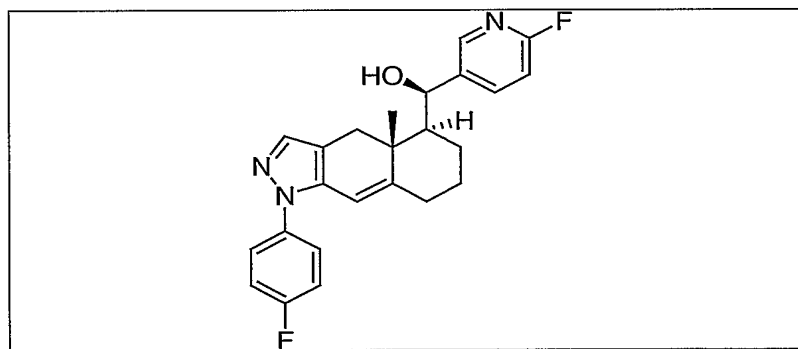


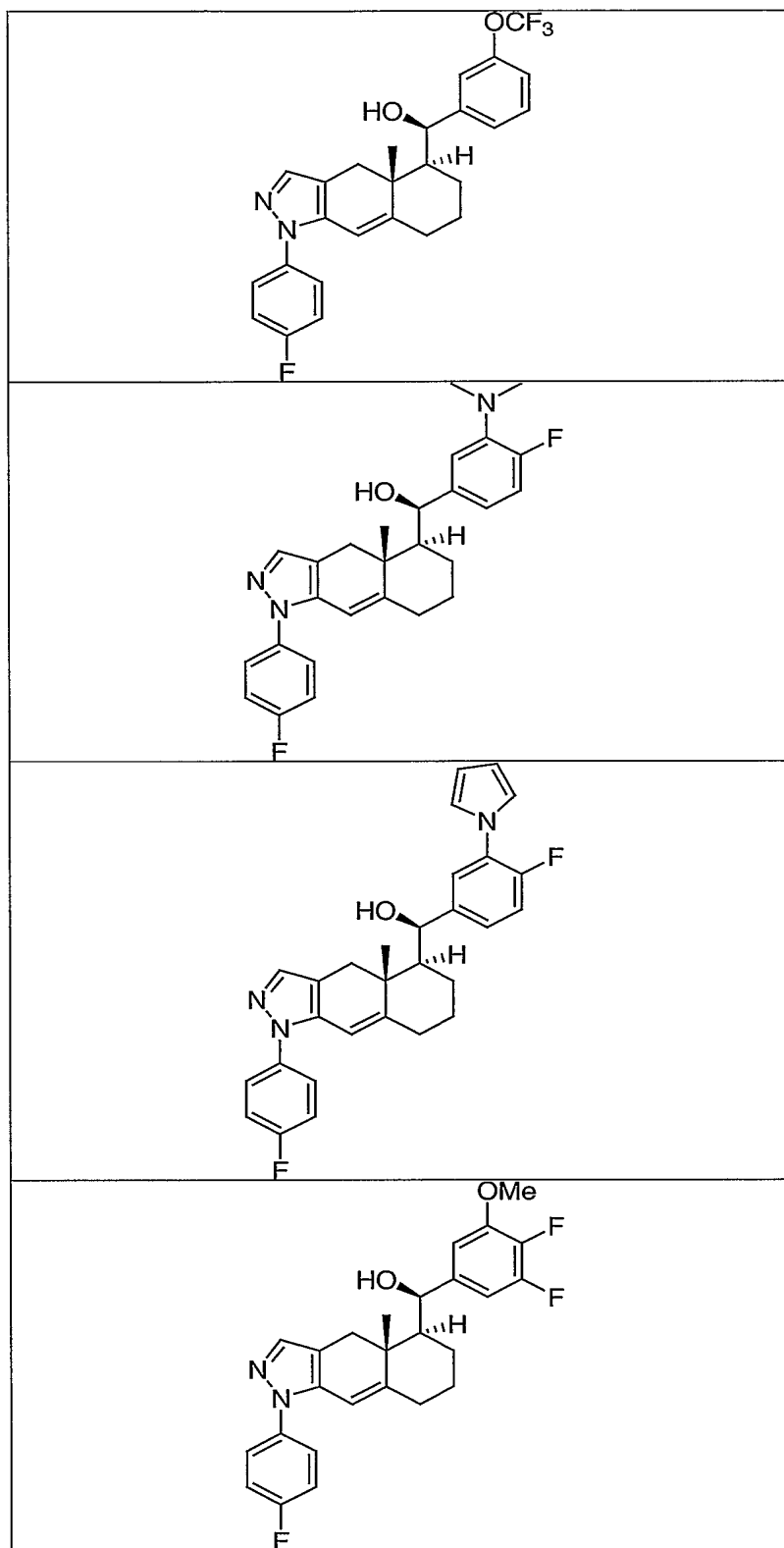


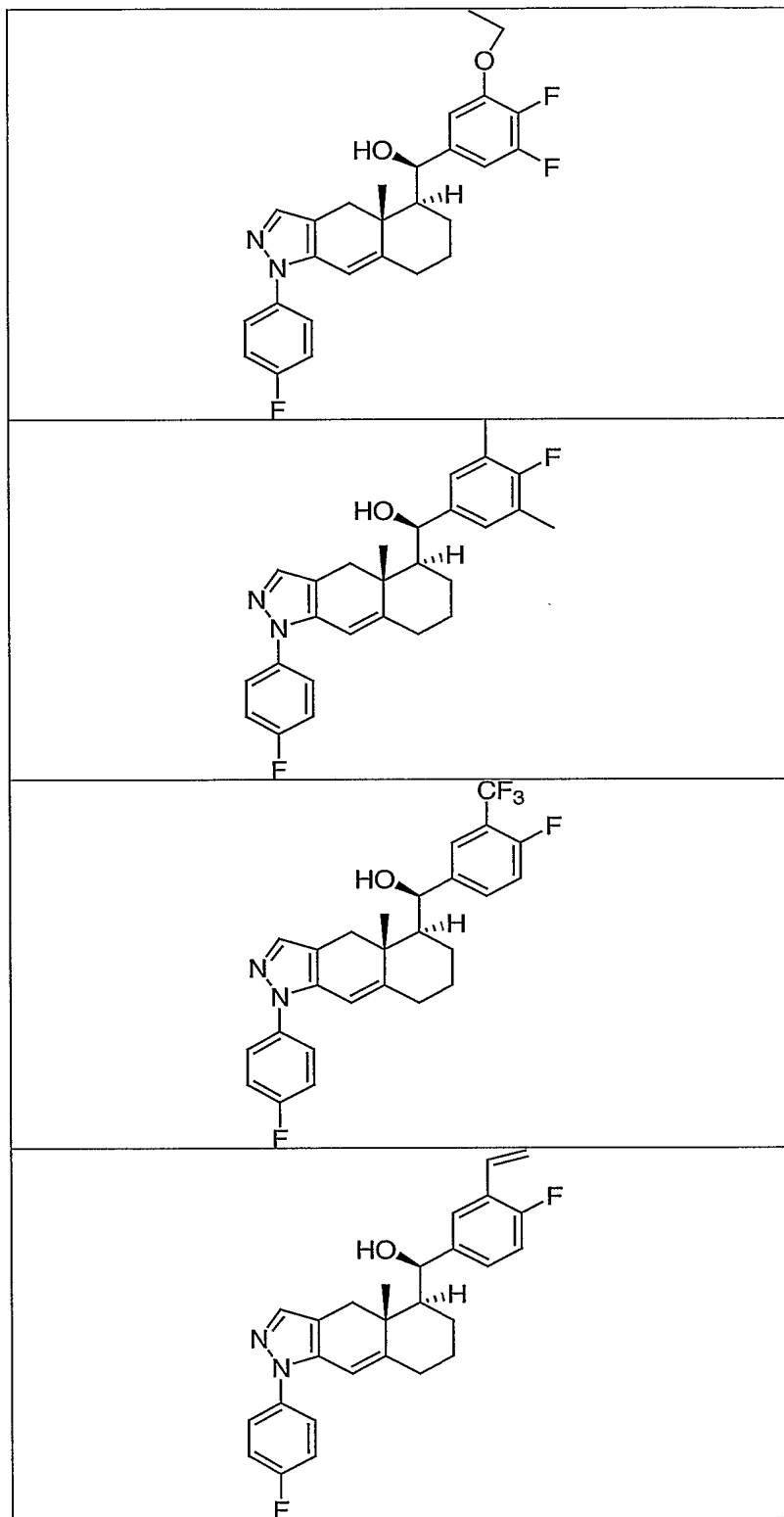


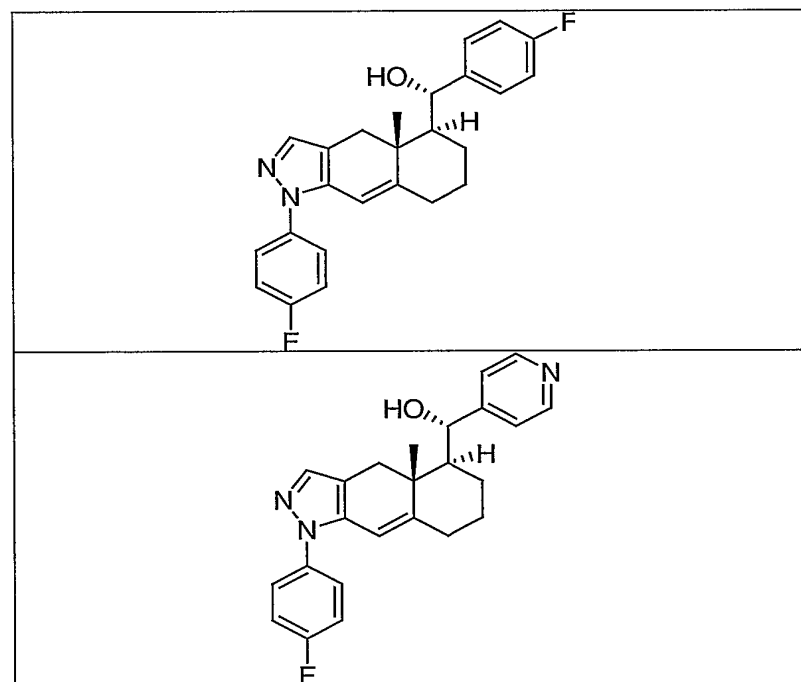
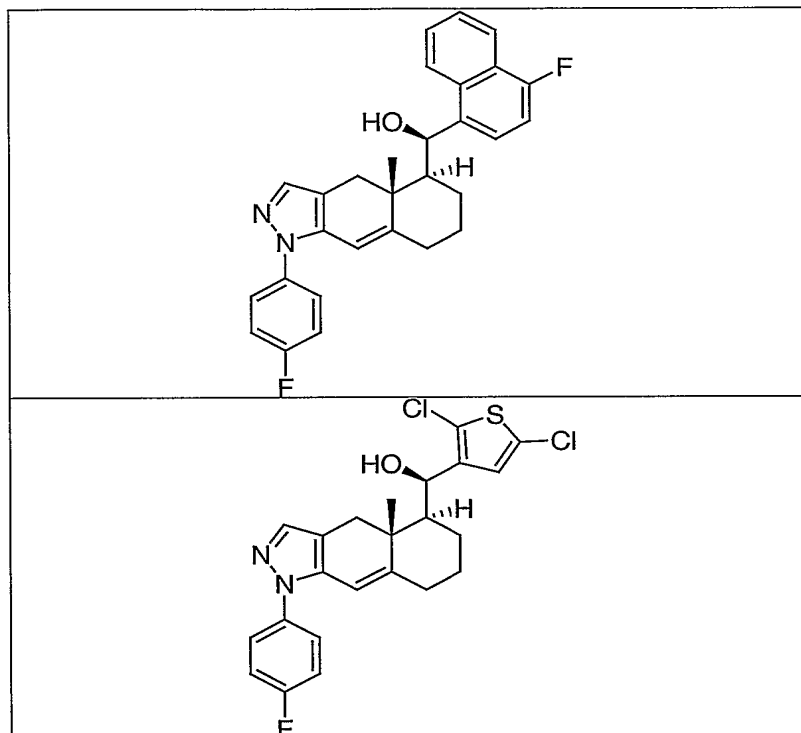
or a pharmaceutically acceptable salt of any of the above.

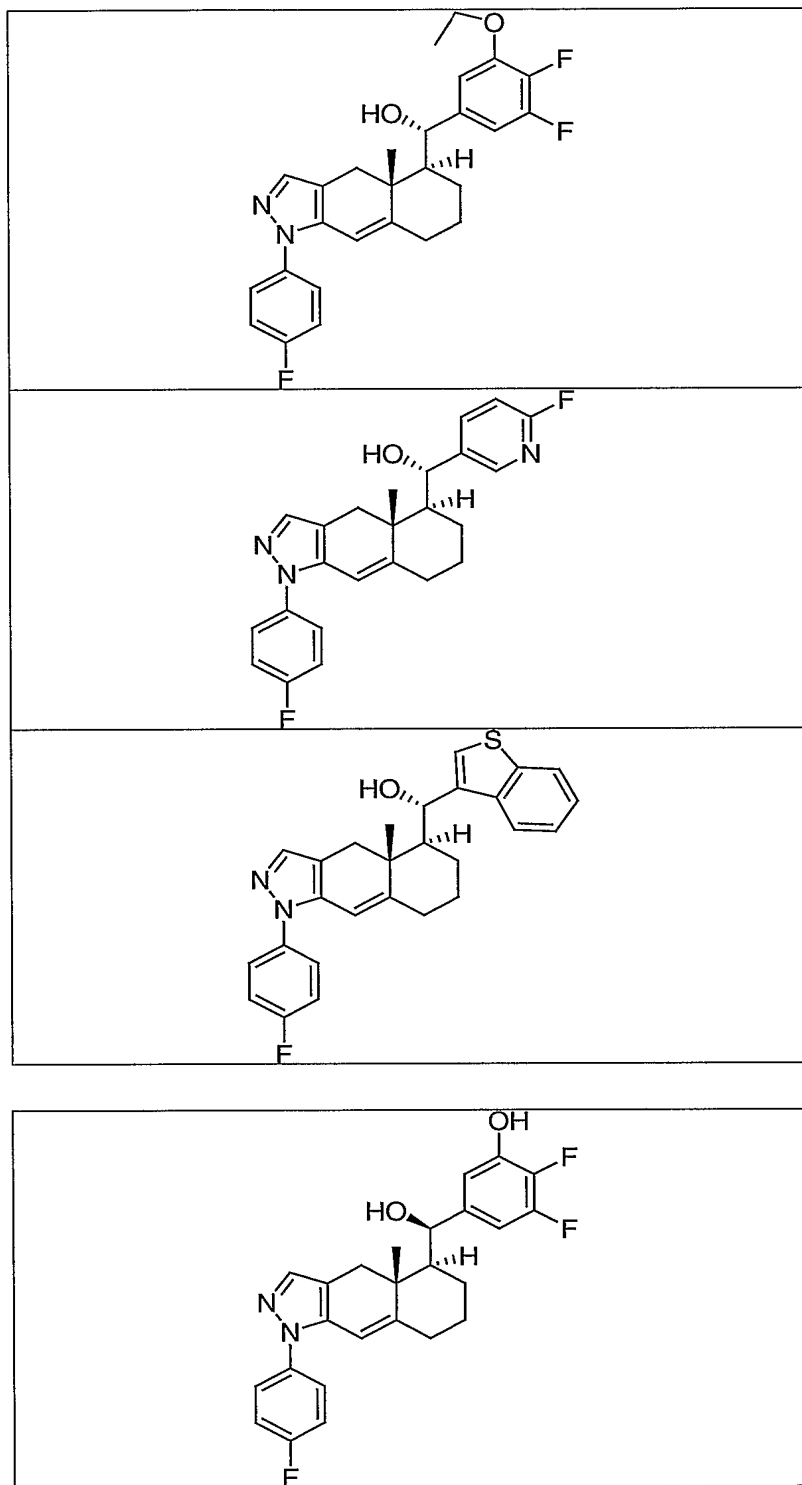
18. A compound according to Claim 1 selected from one of the
5 following tables:

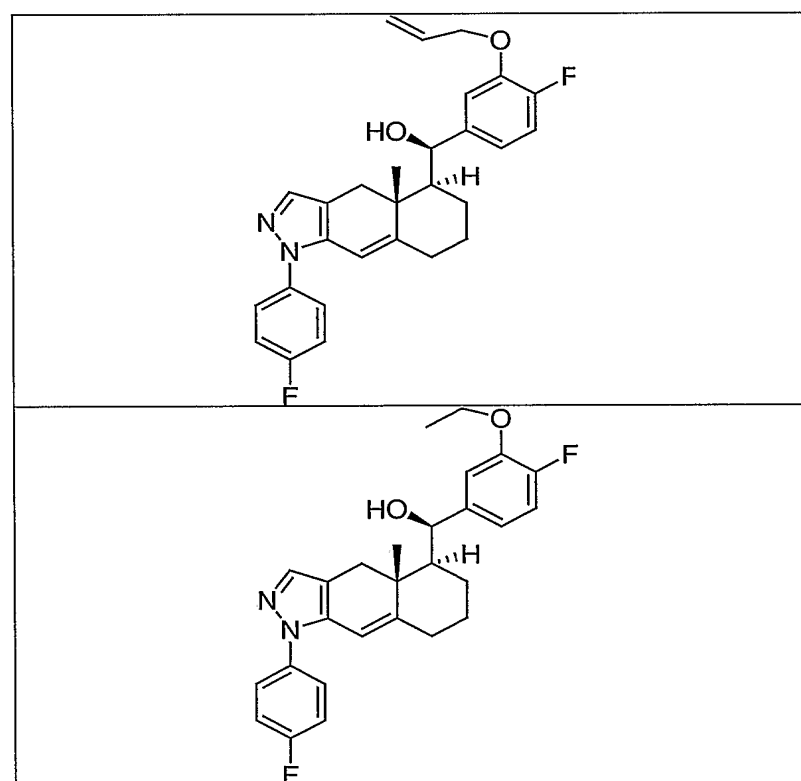
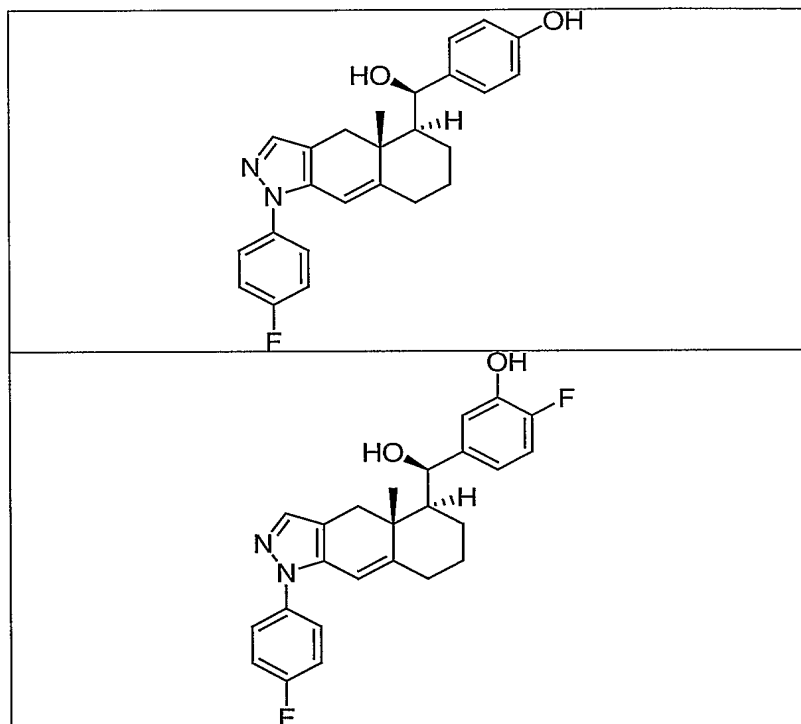


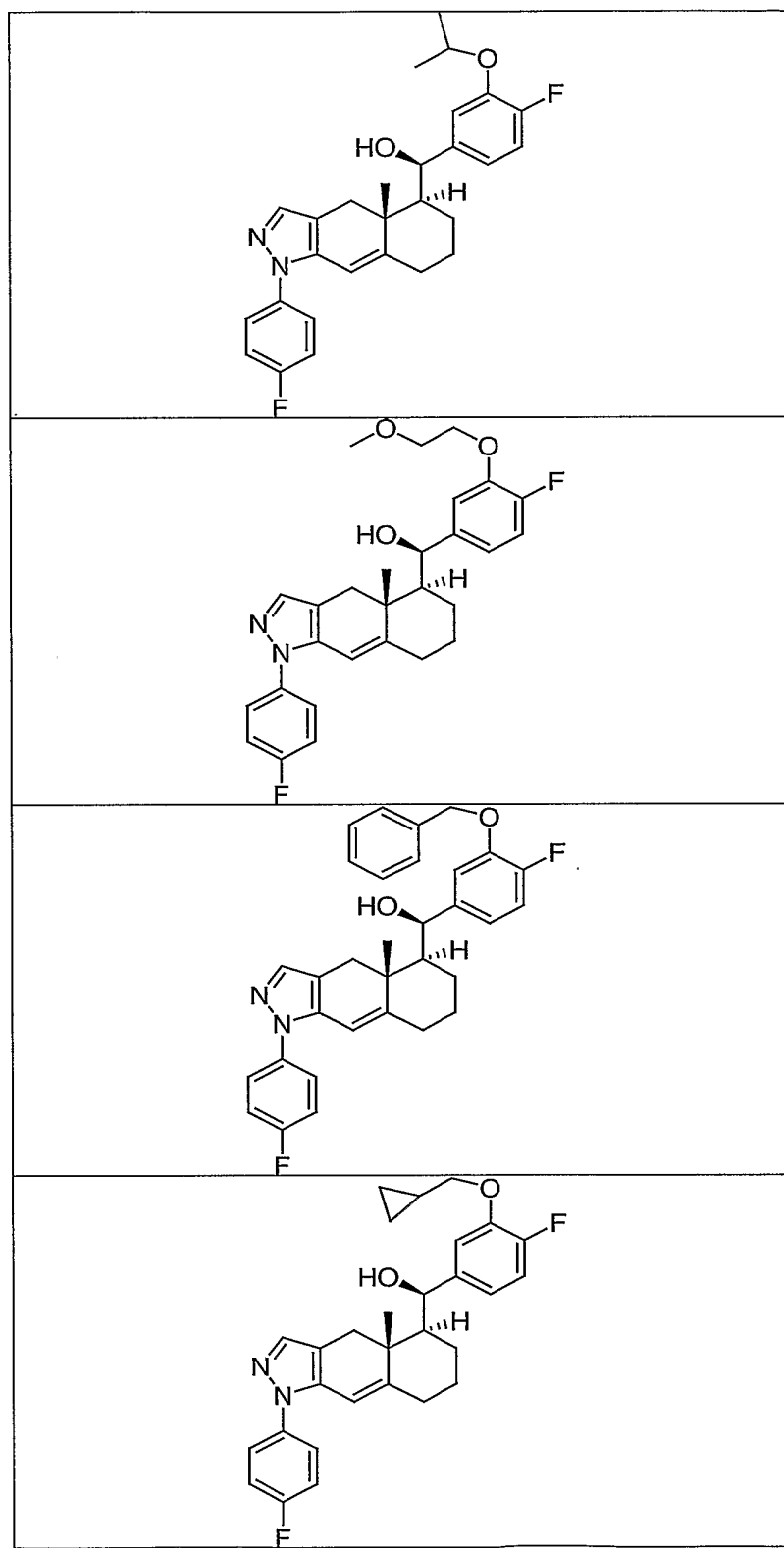


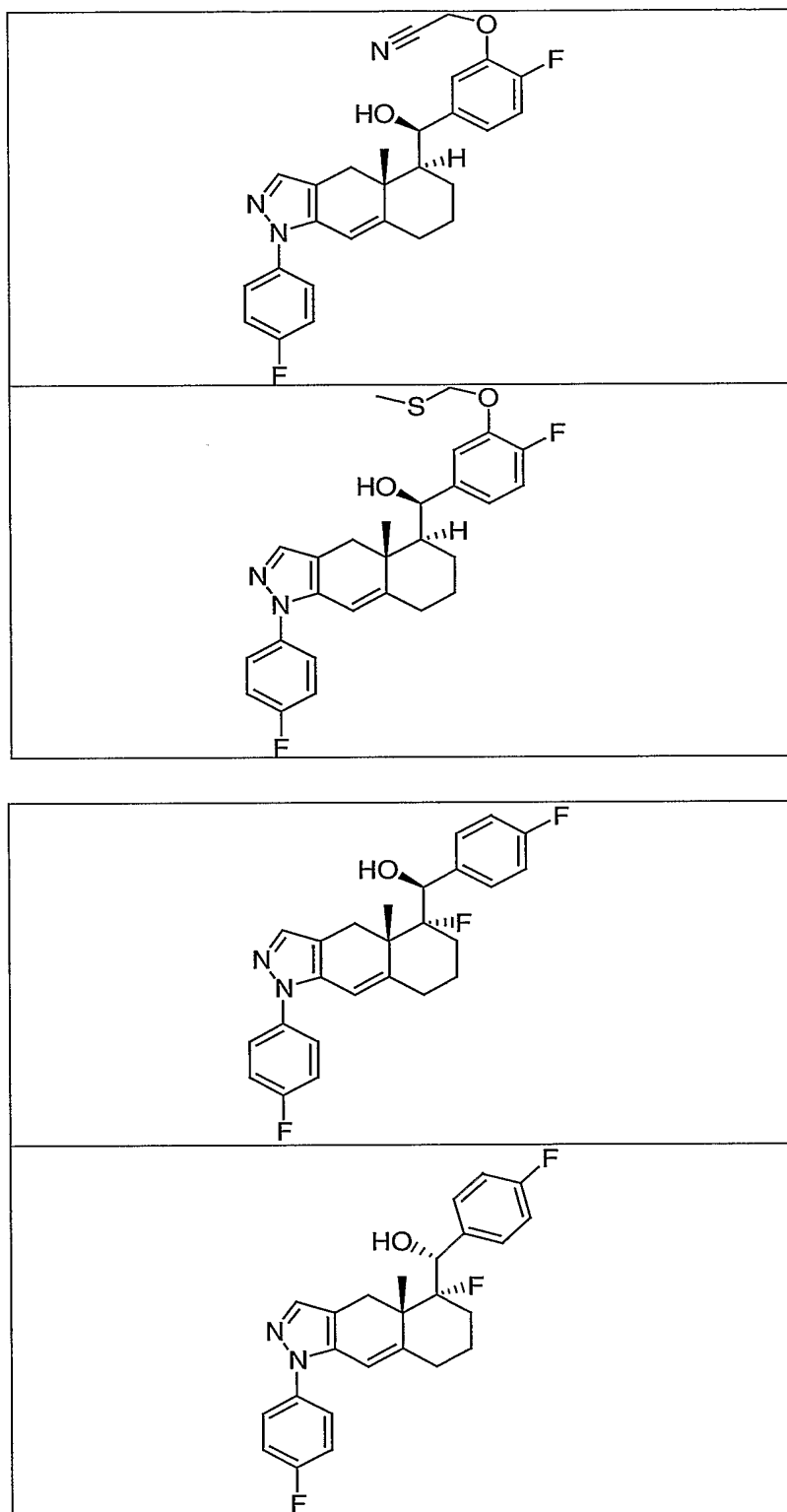


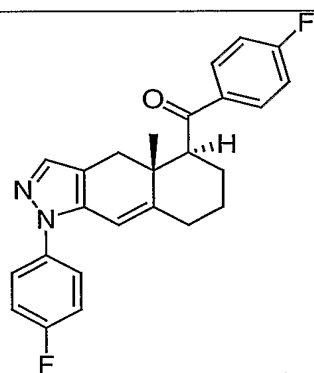
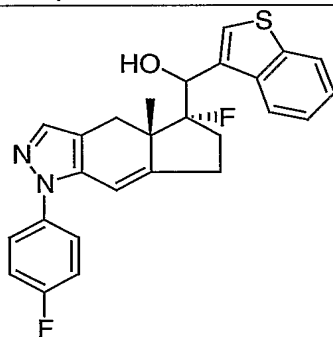
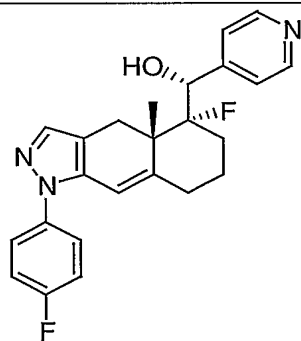
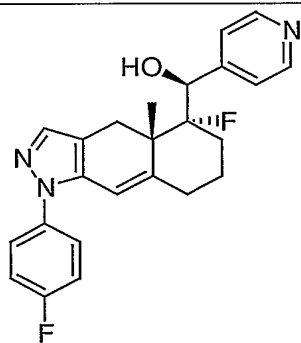


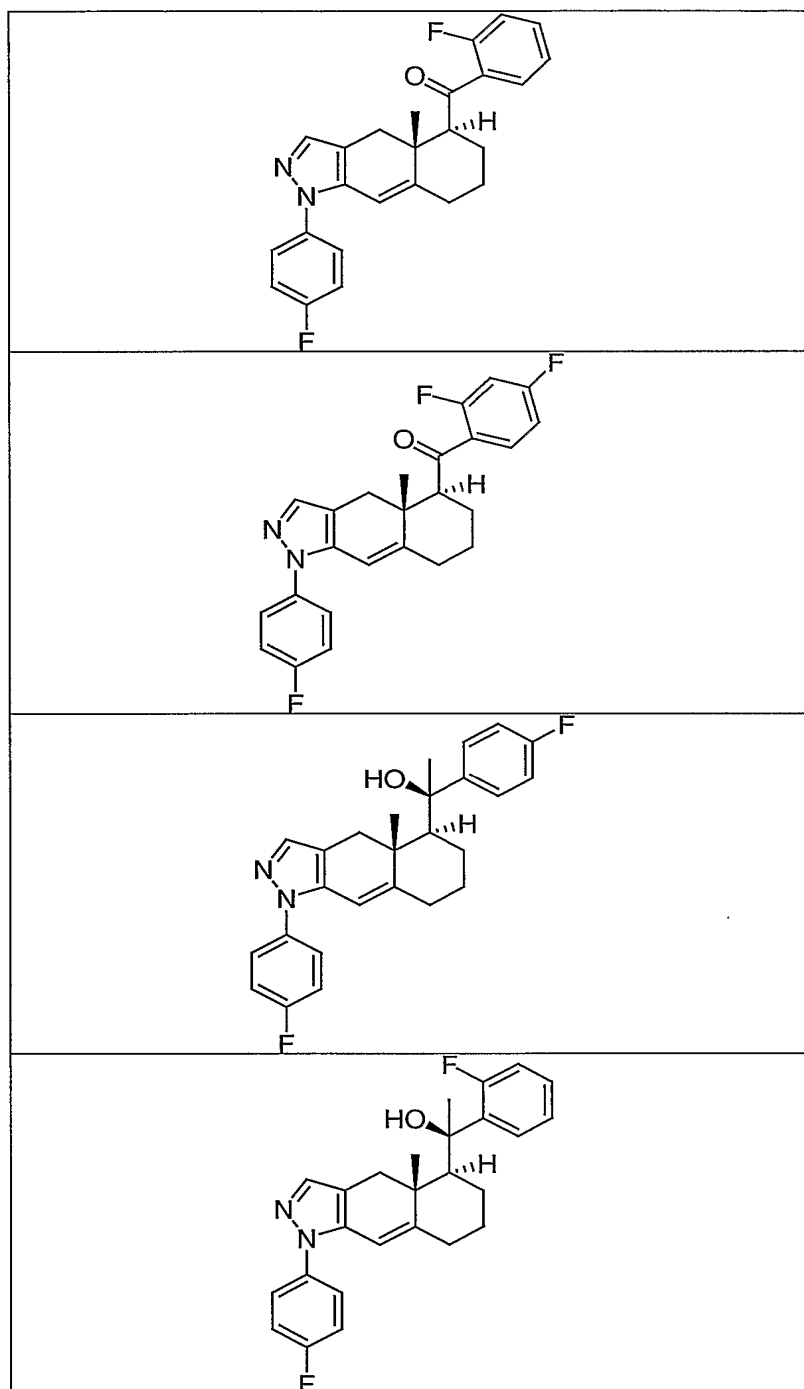


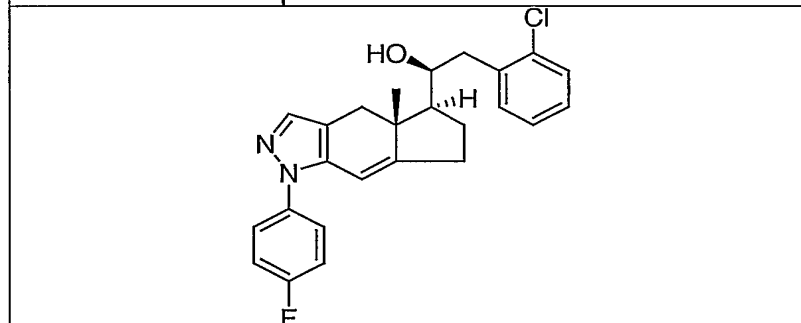
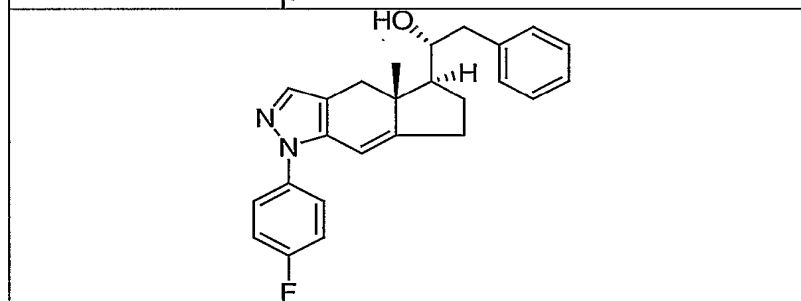
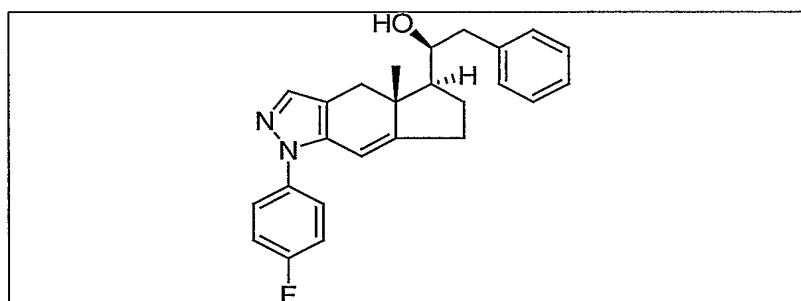
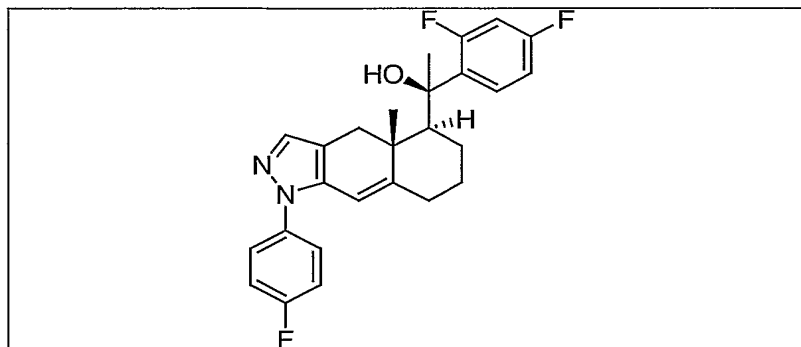


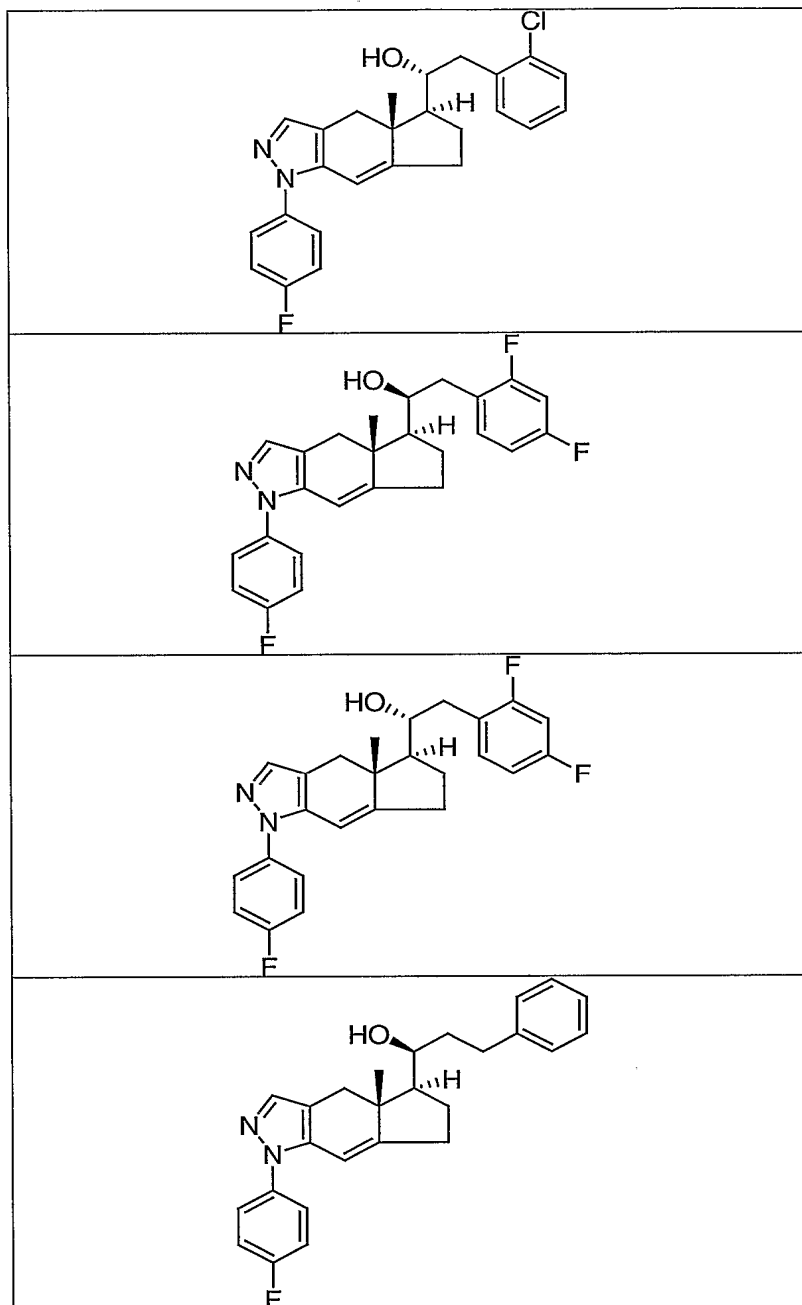


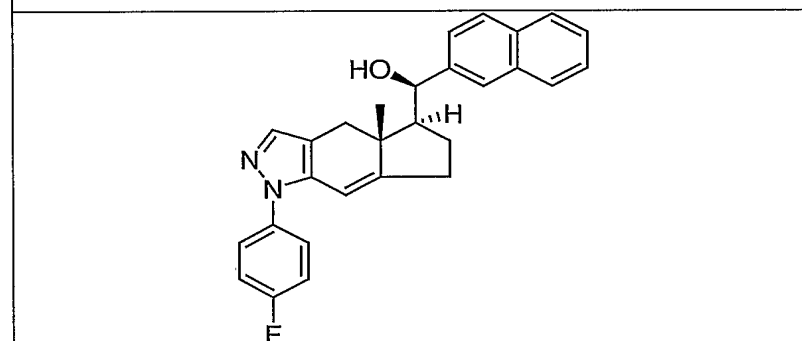
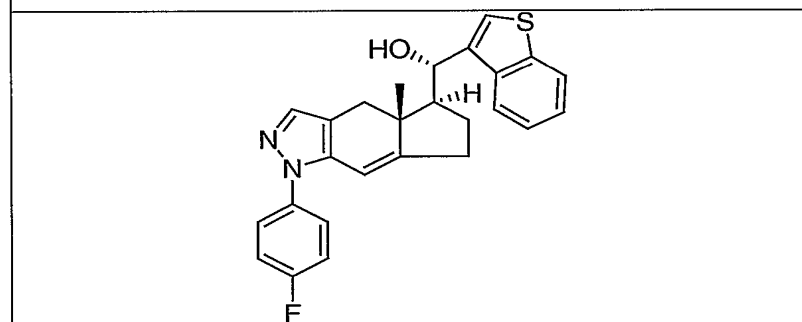
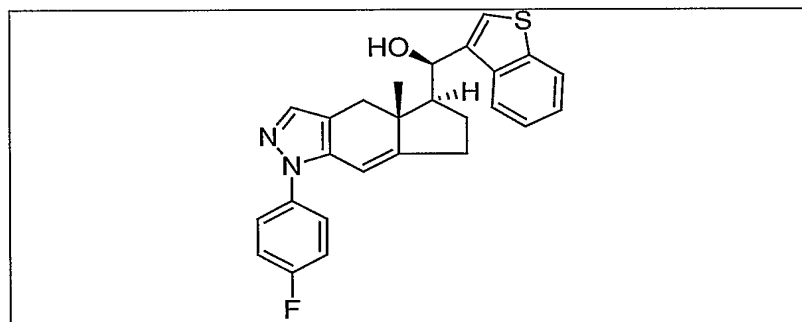
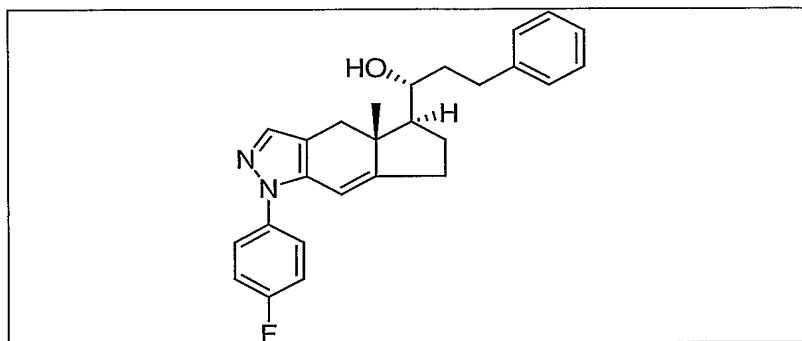


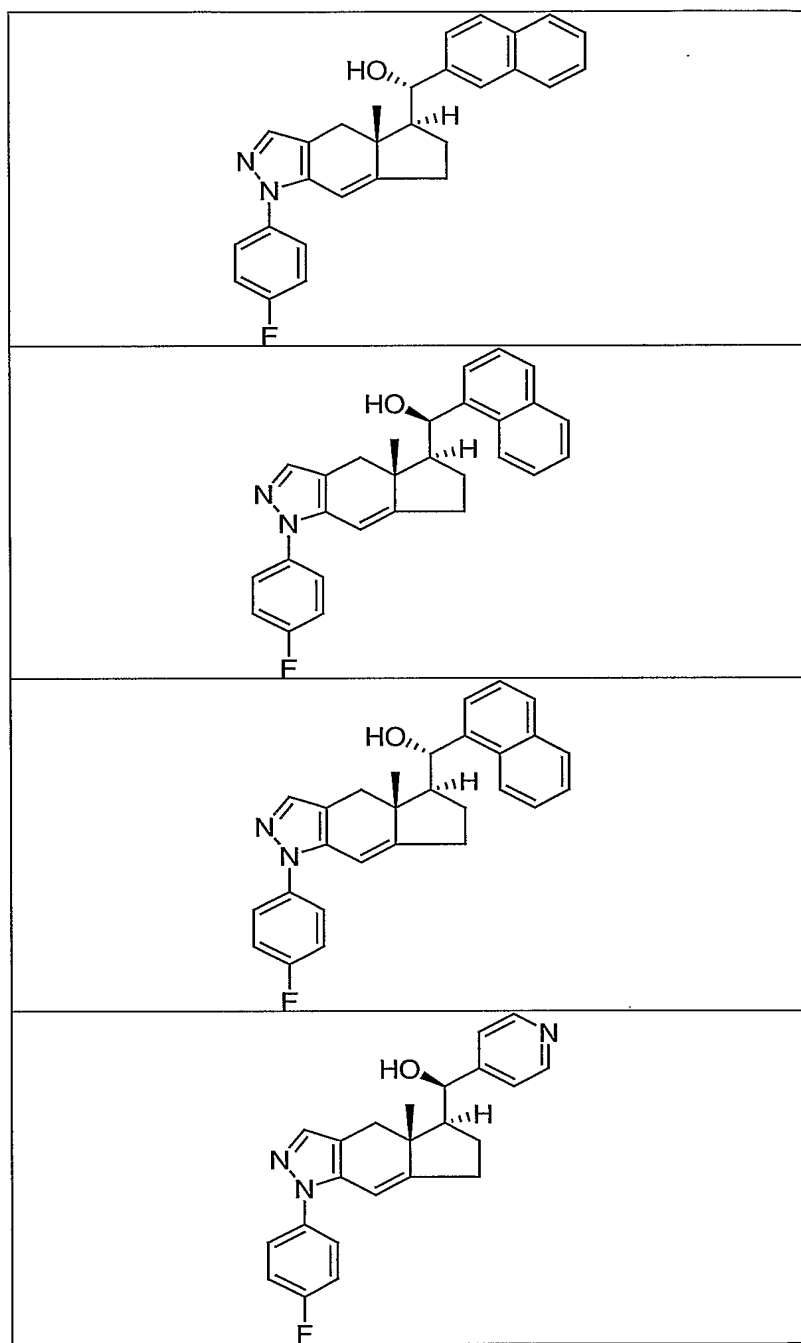


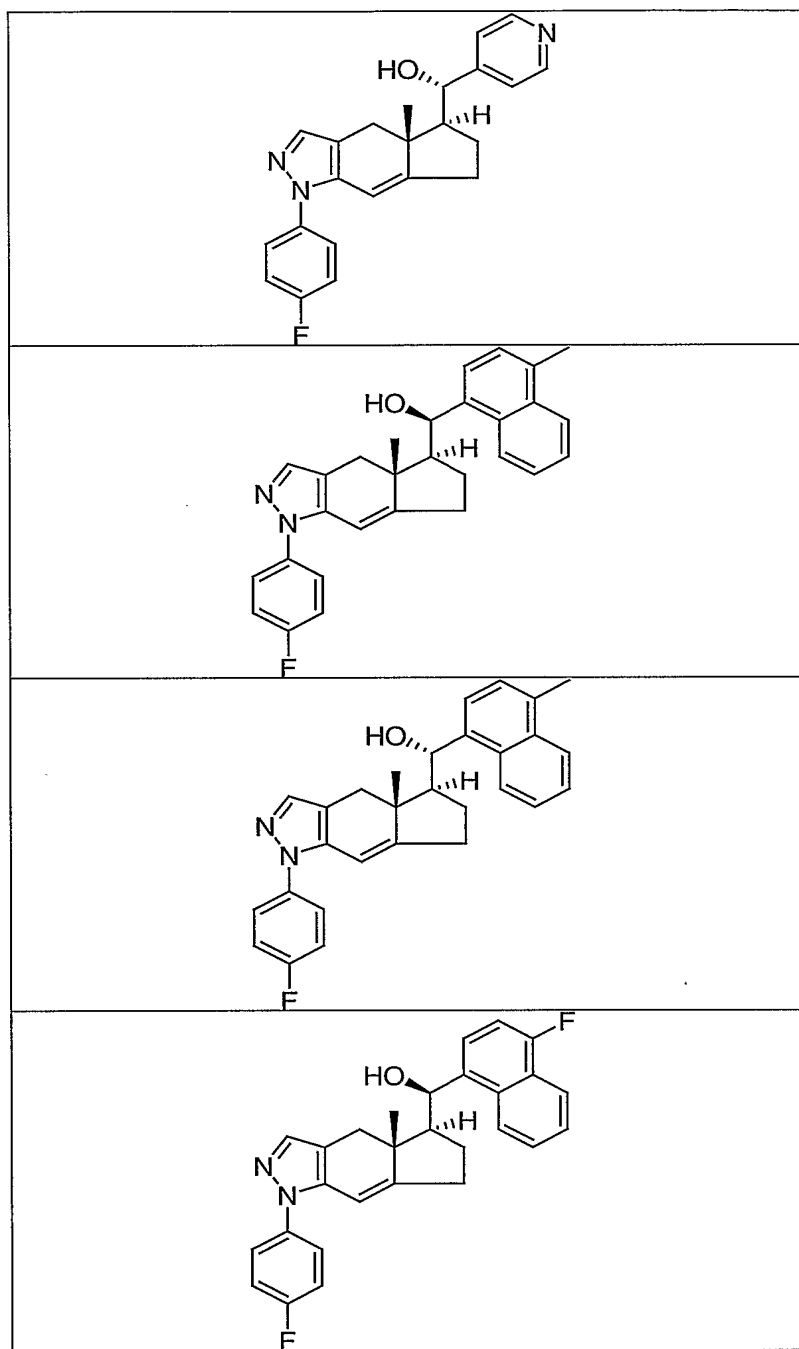


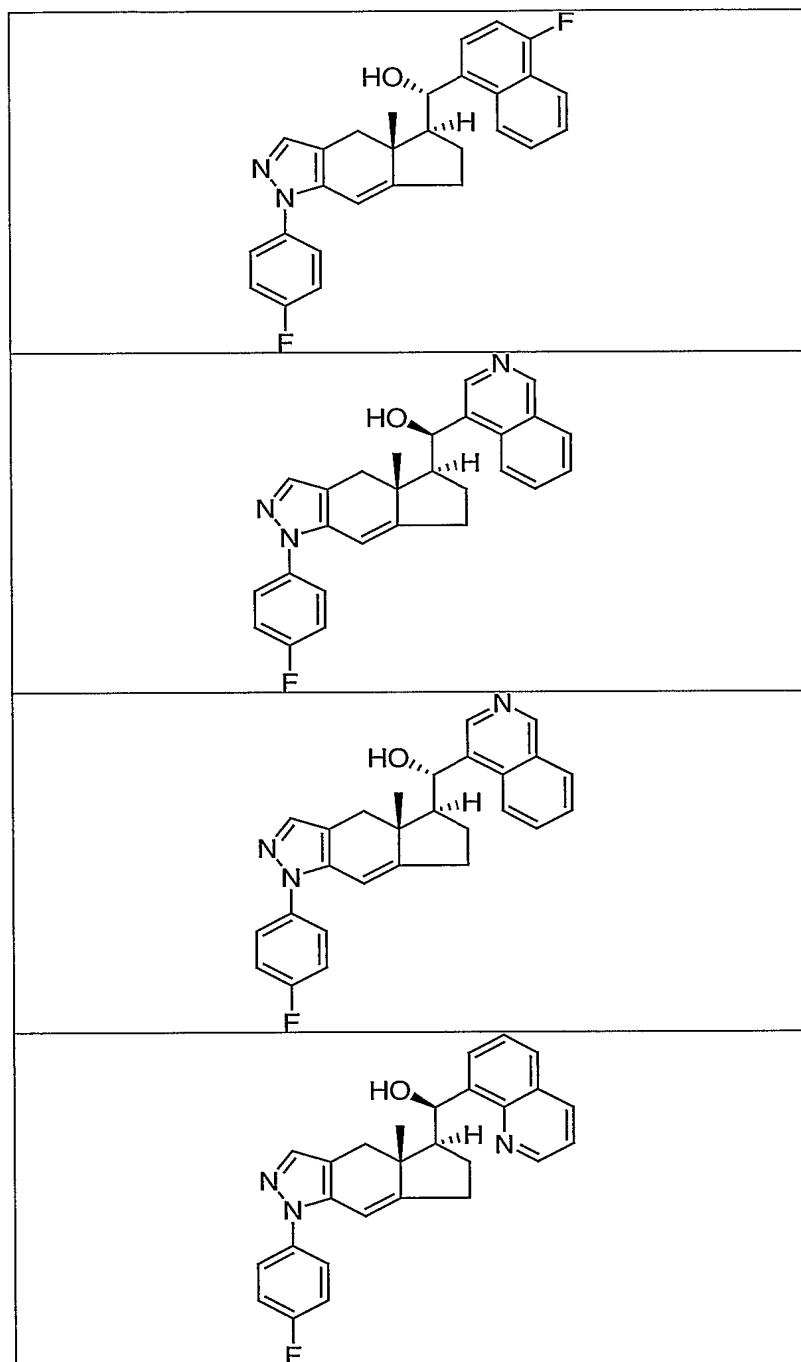


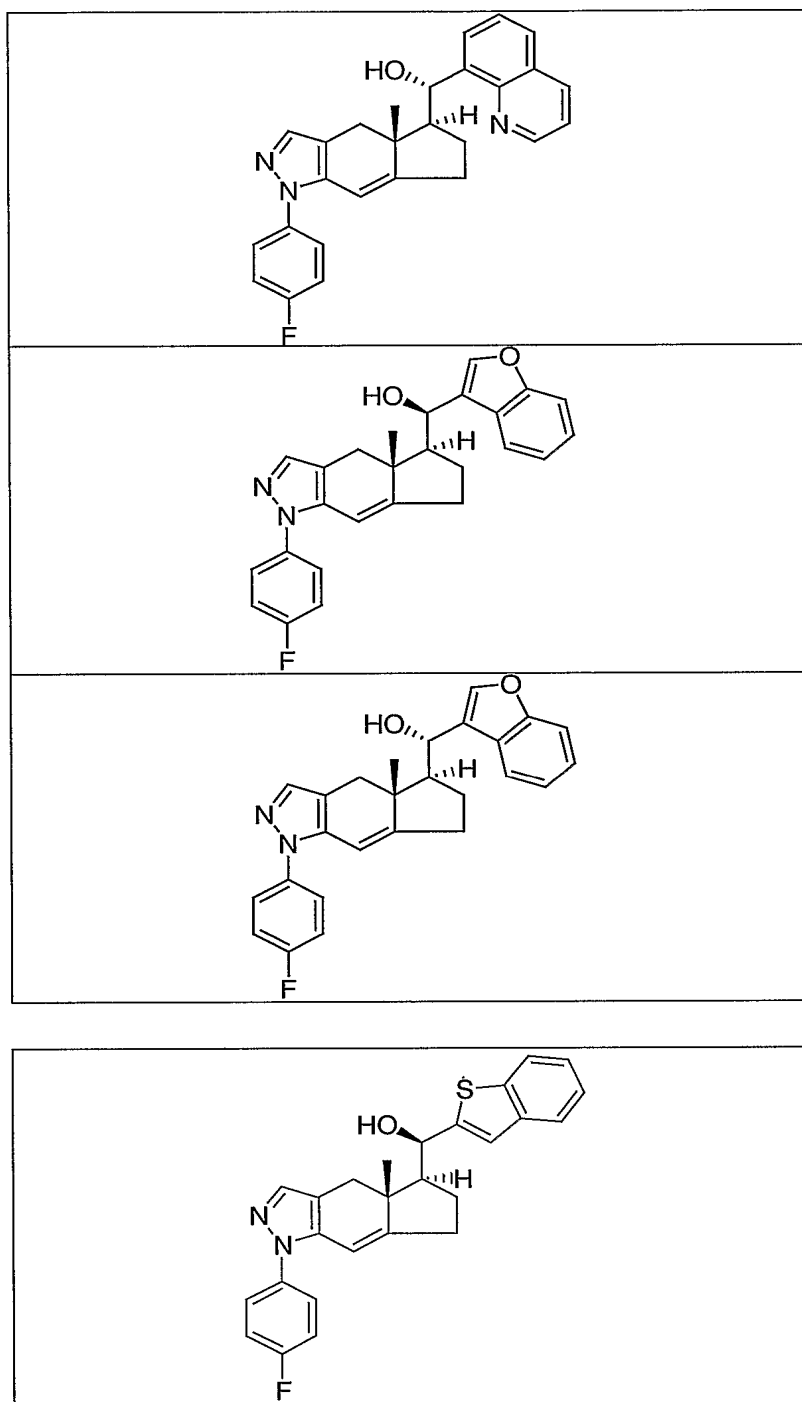


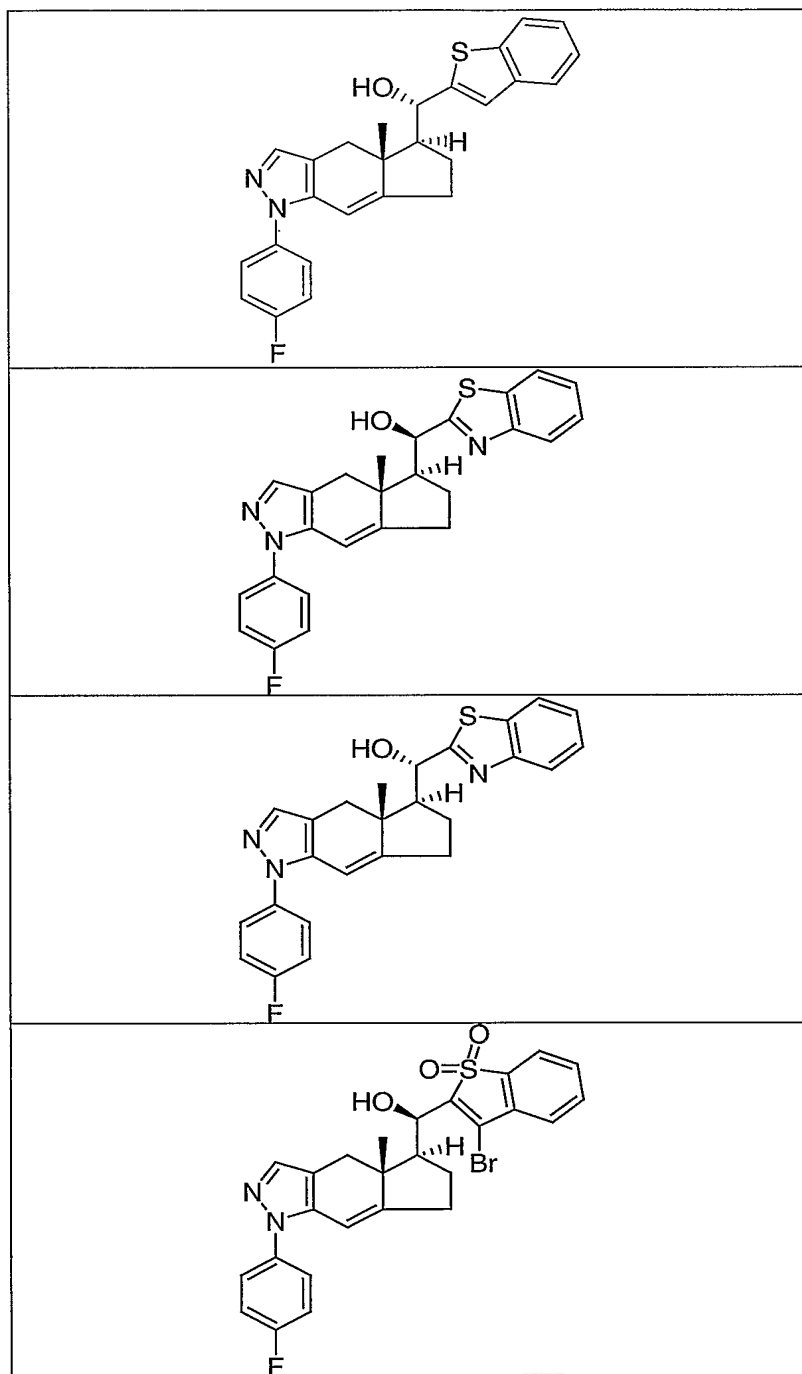


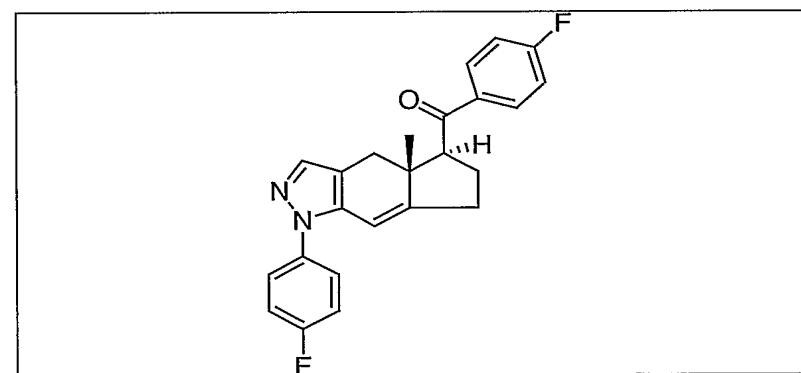
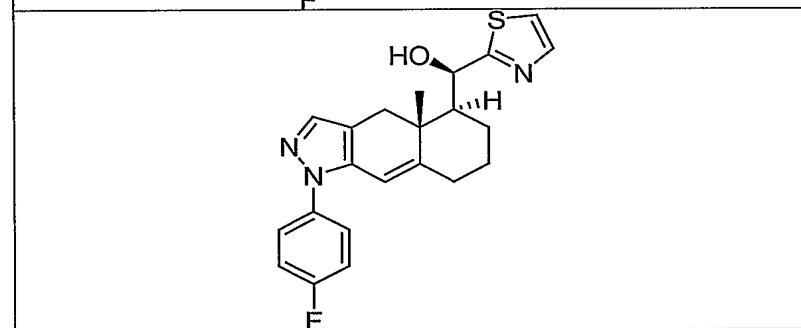
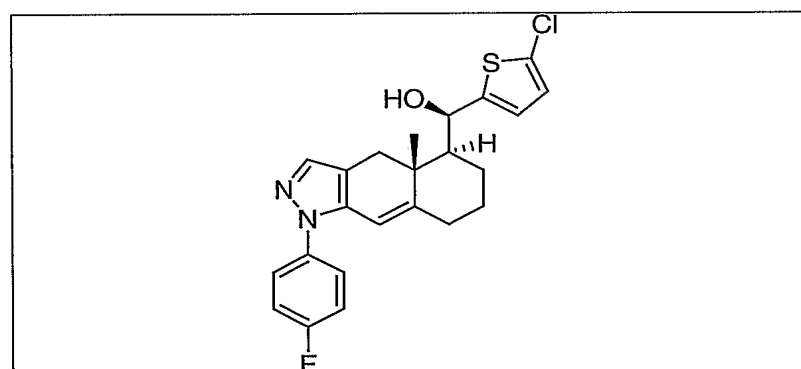
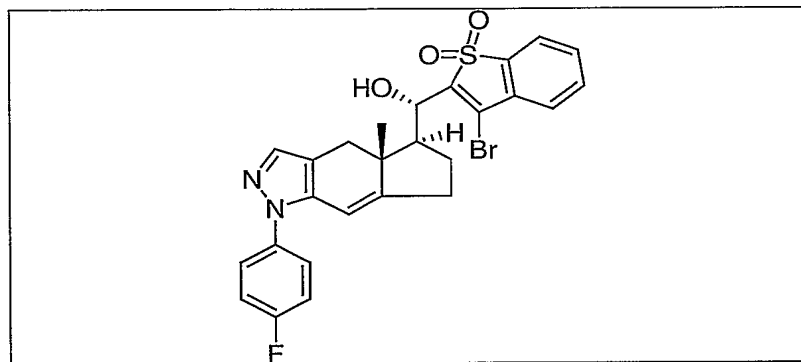


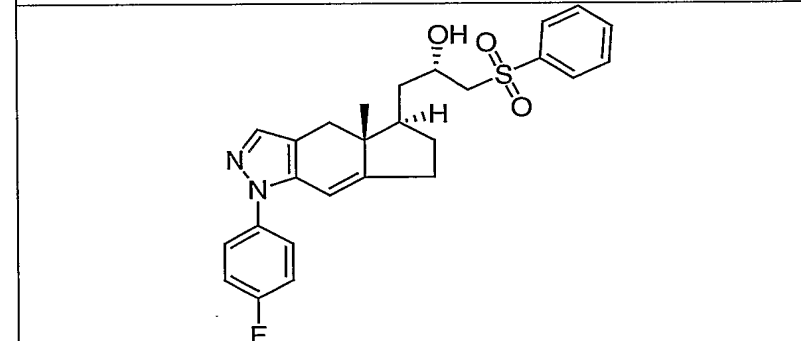
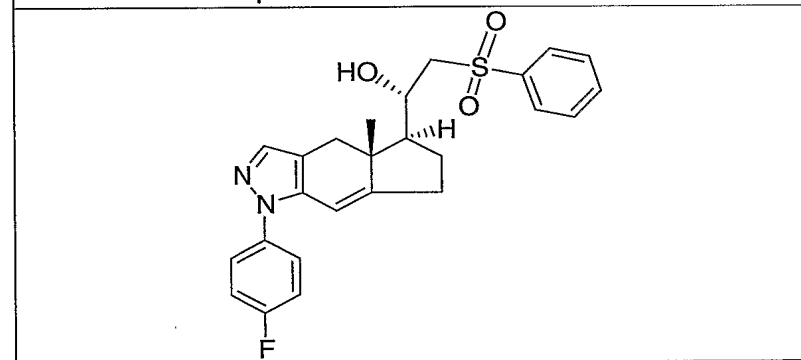
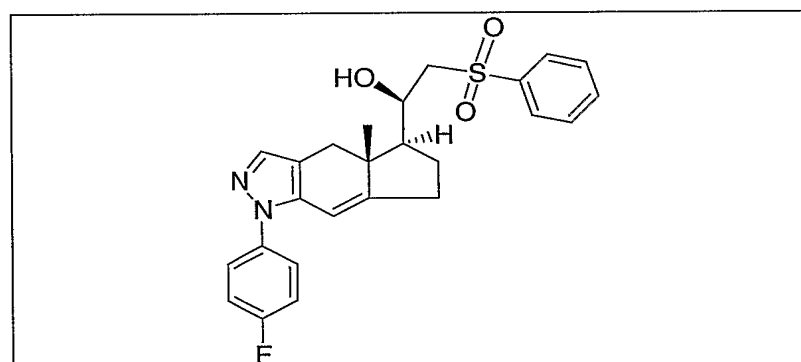
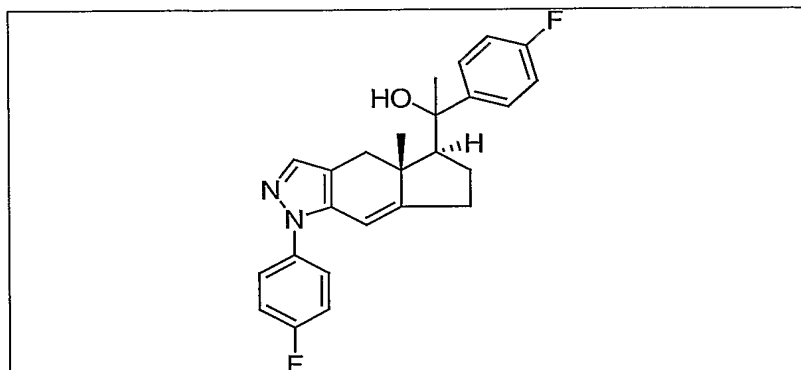


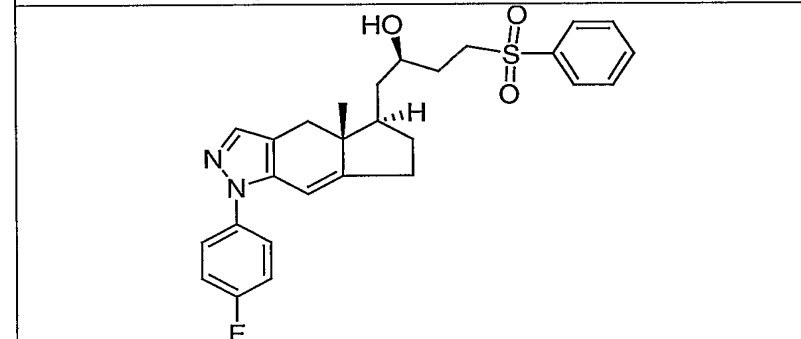
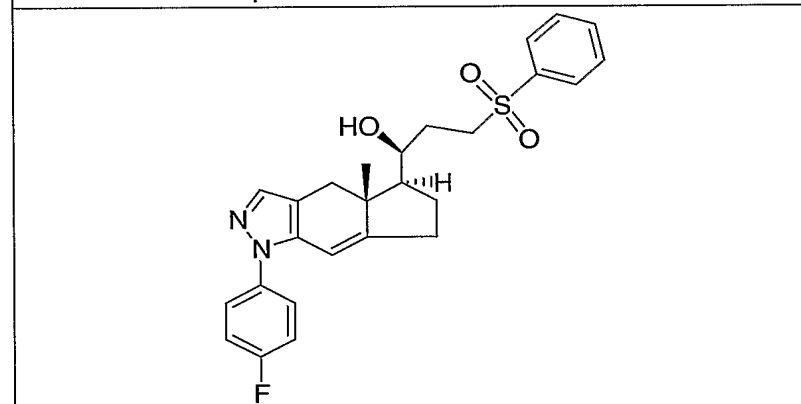
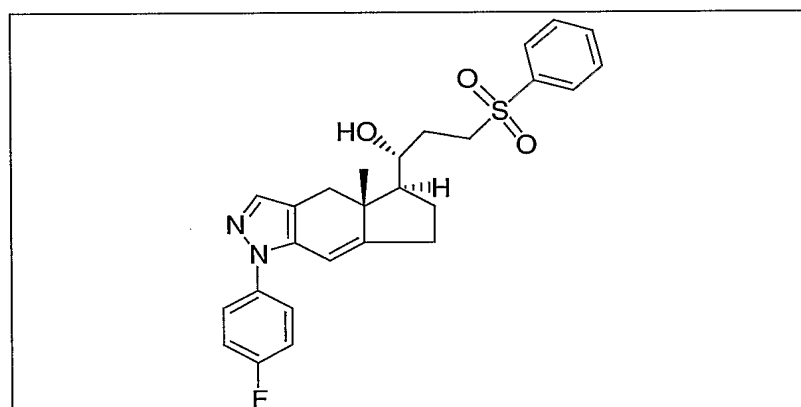
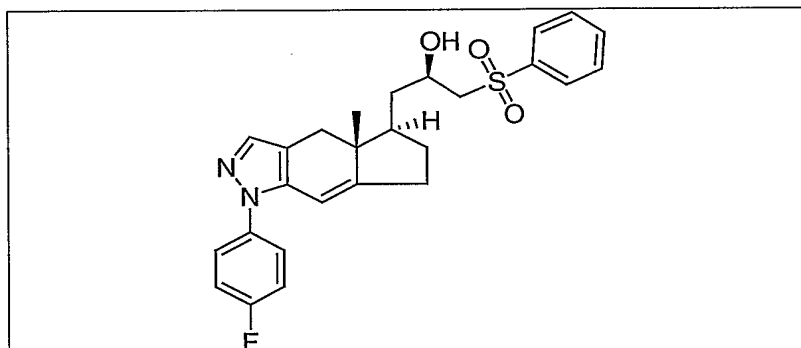


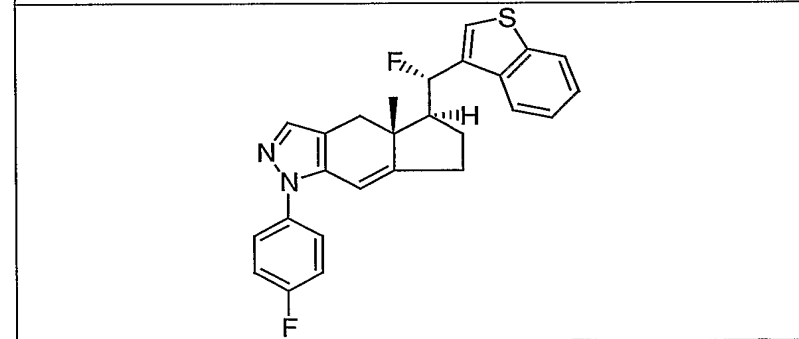
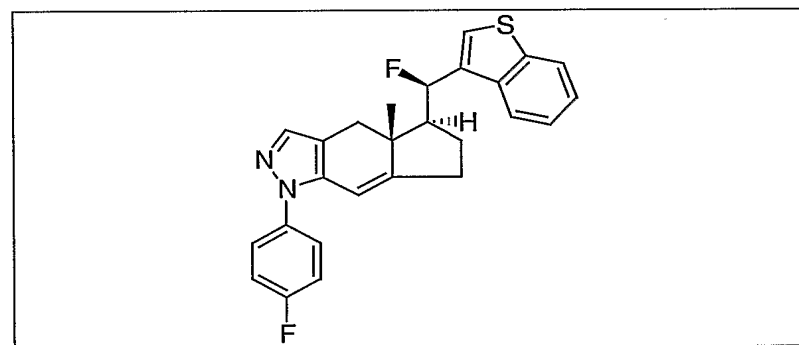
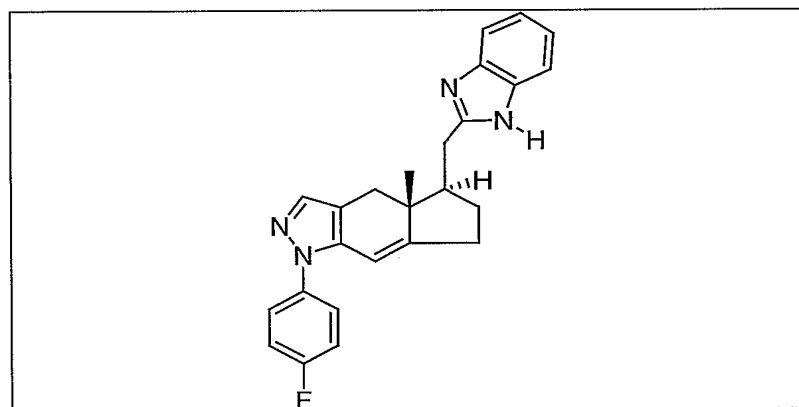
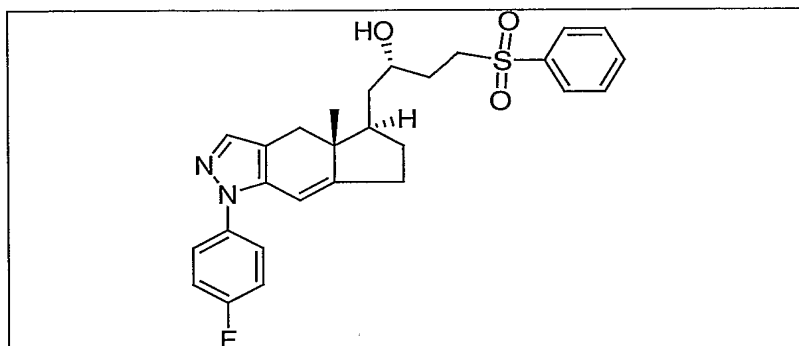


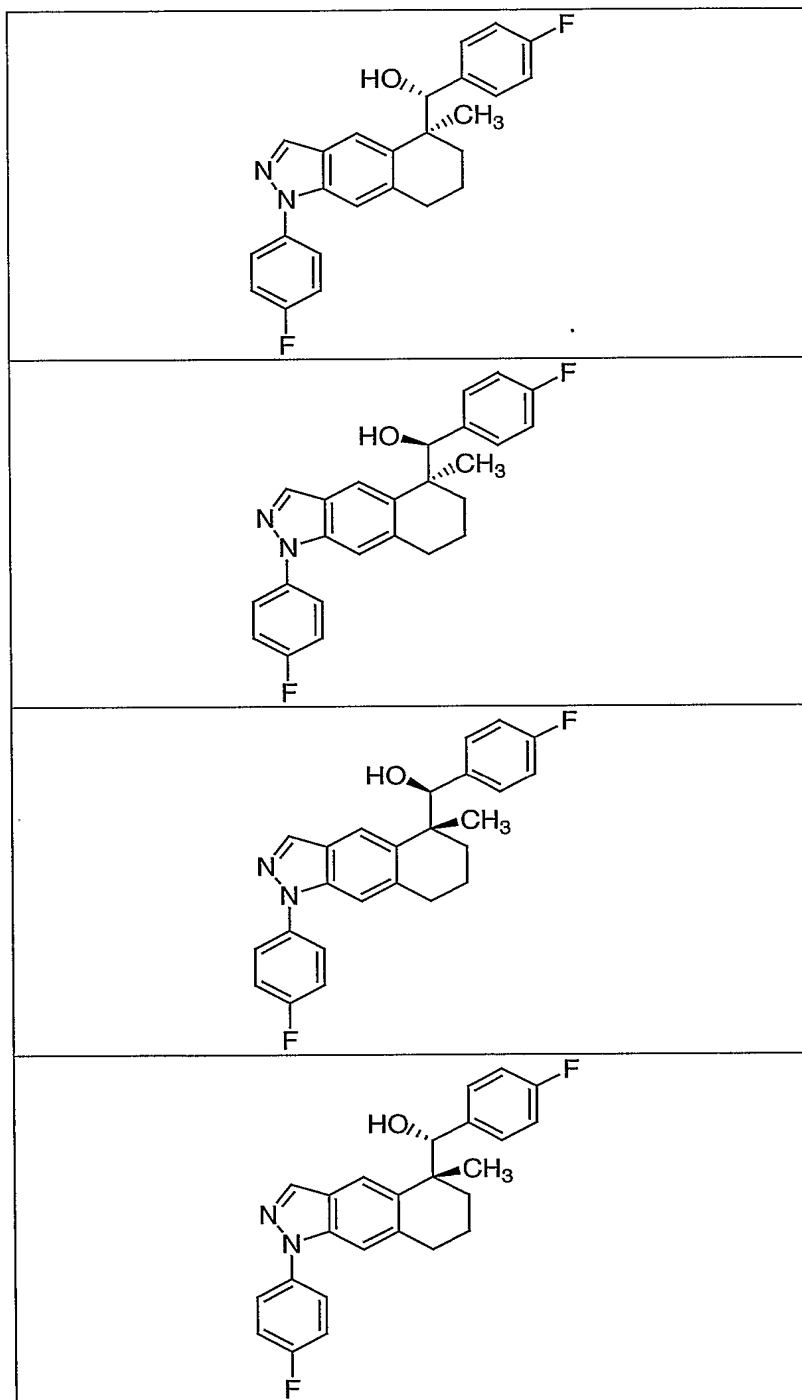


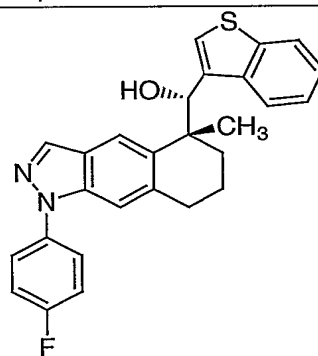
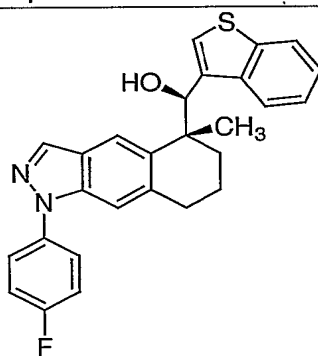
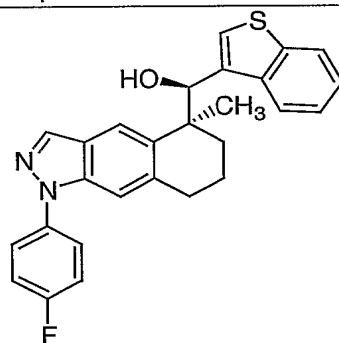
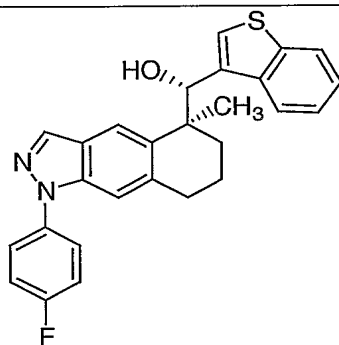


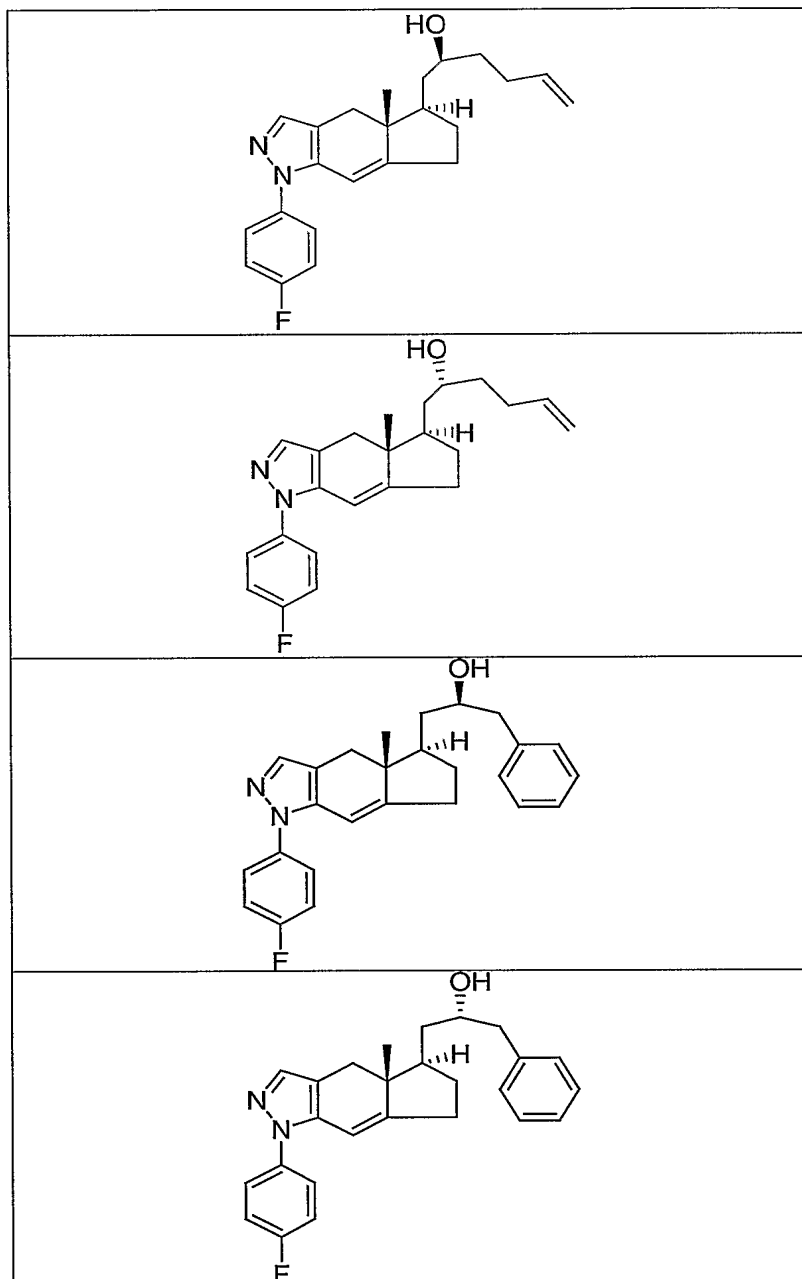


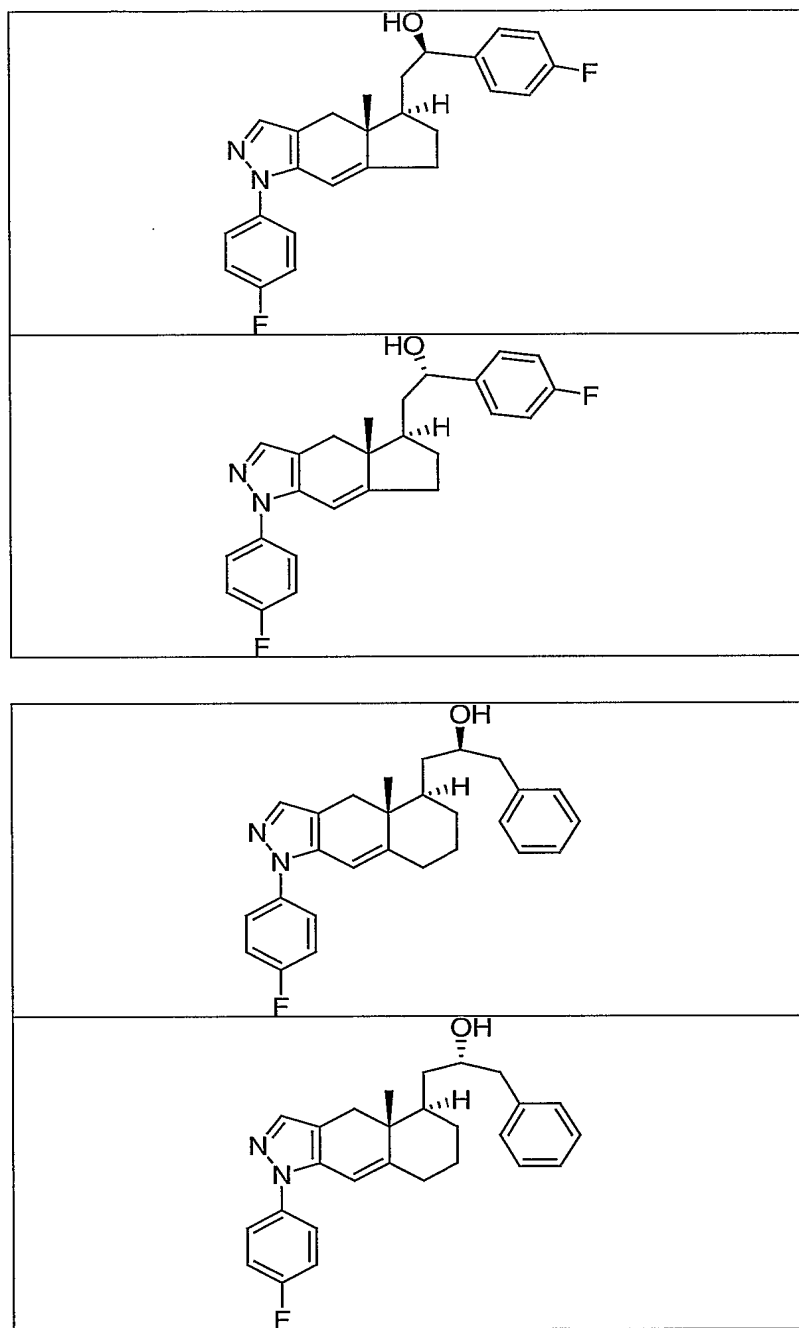


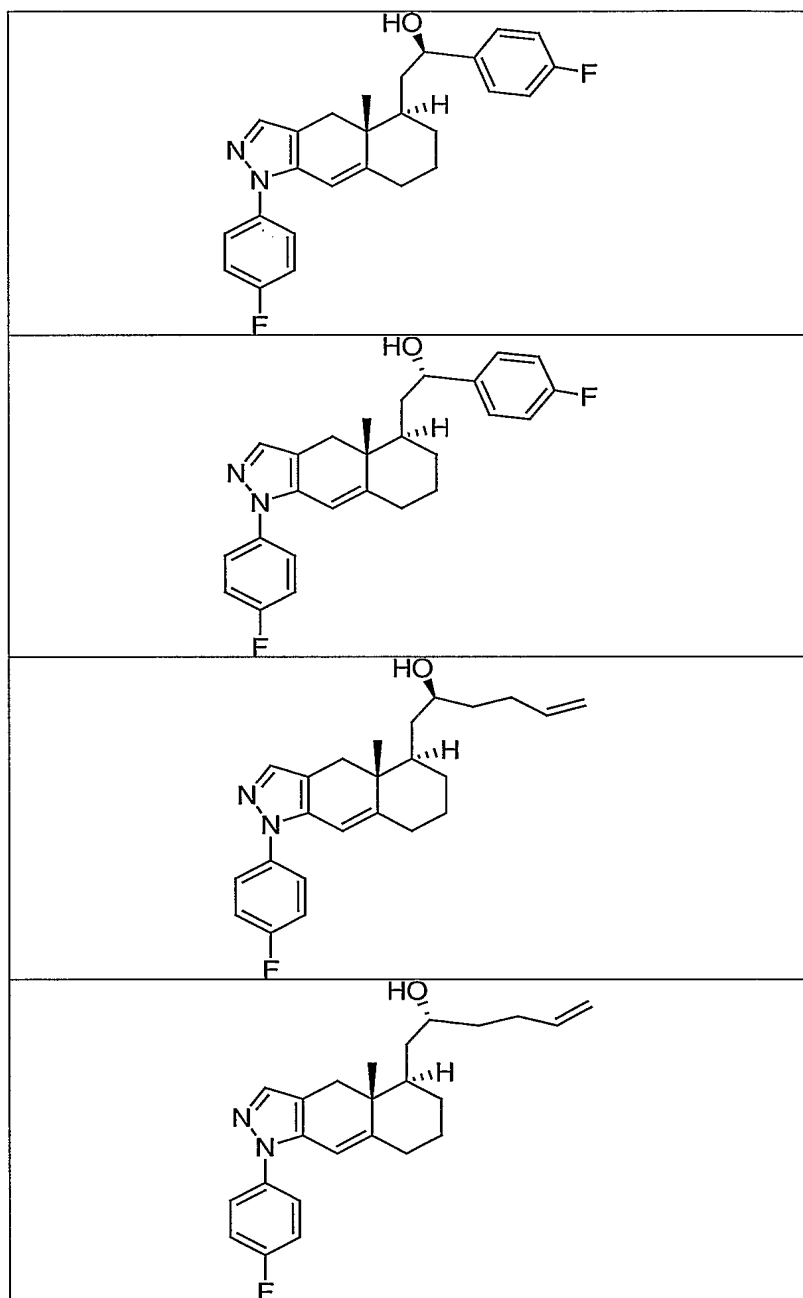


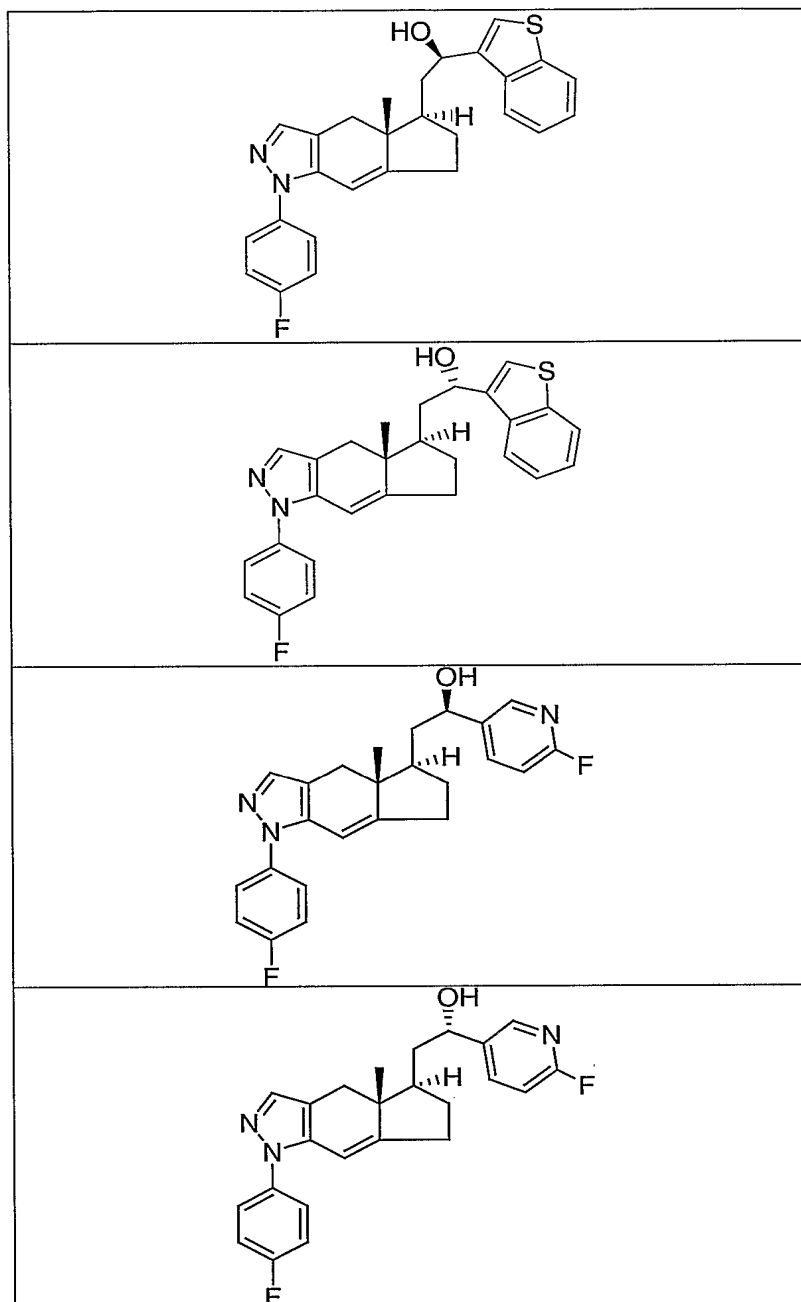


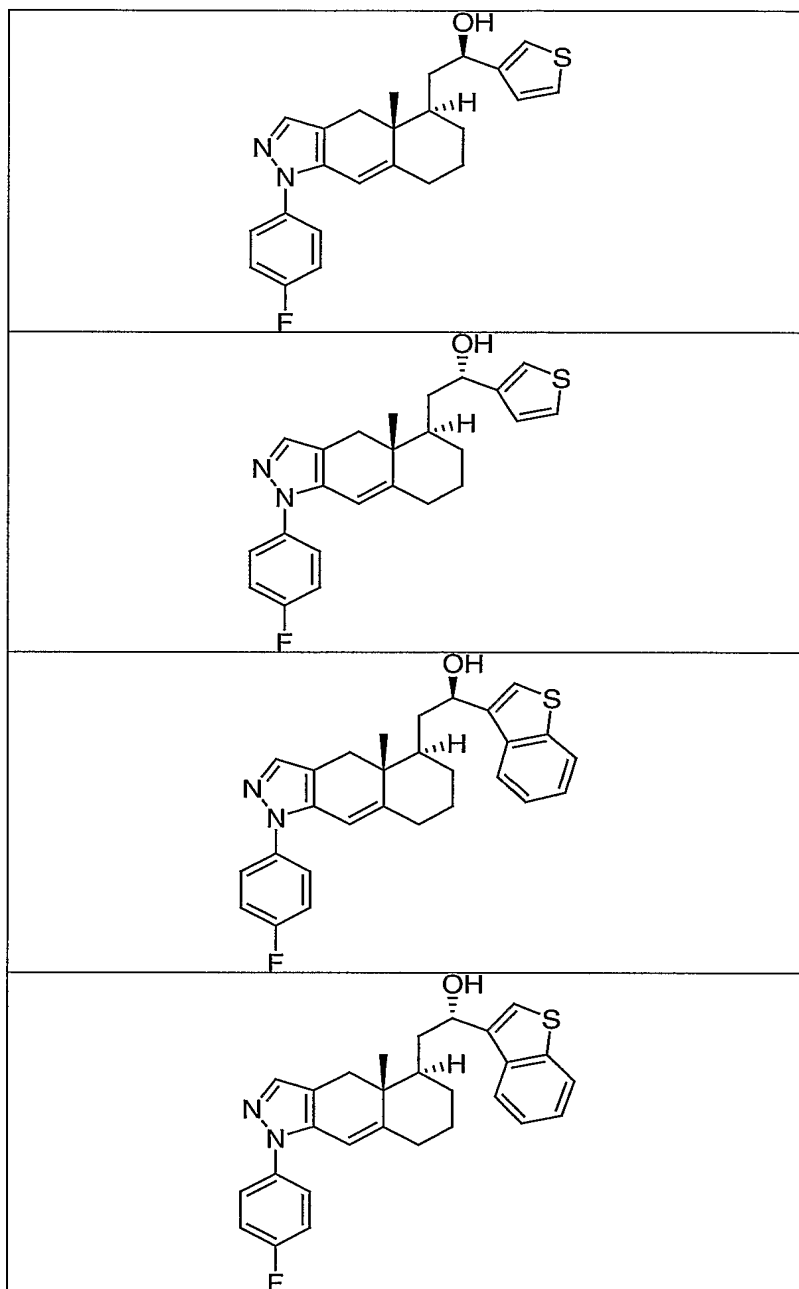


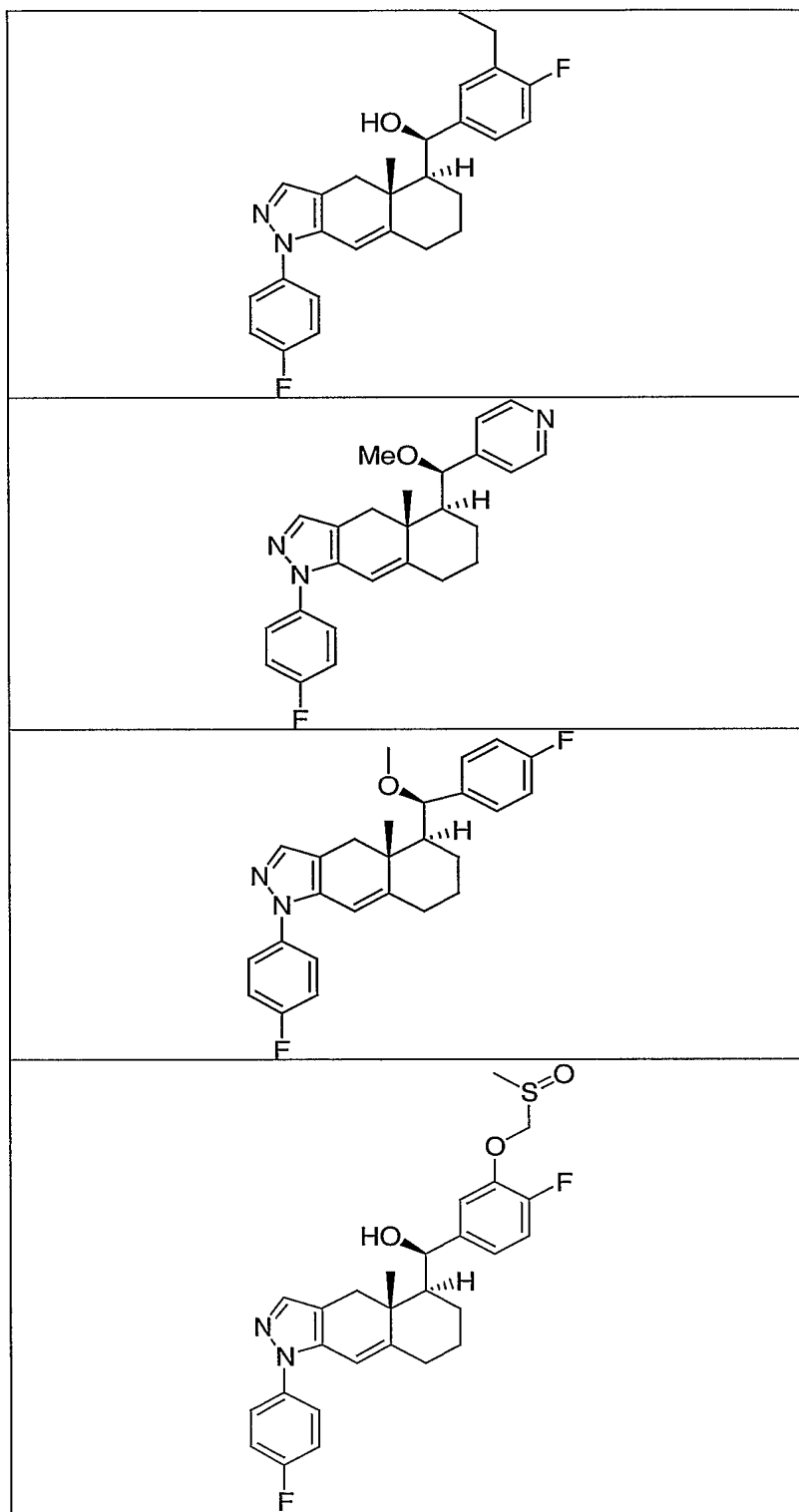


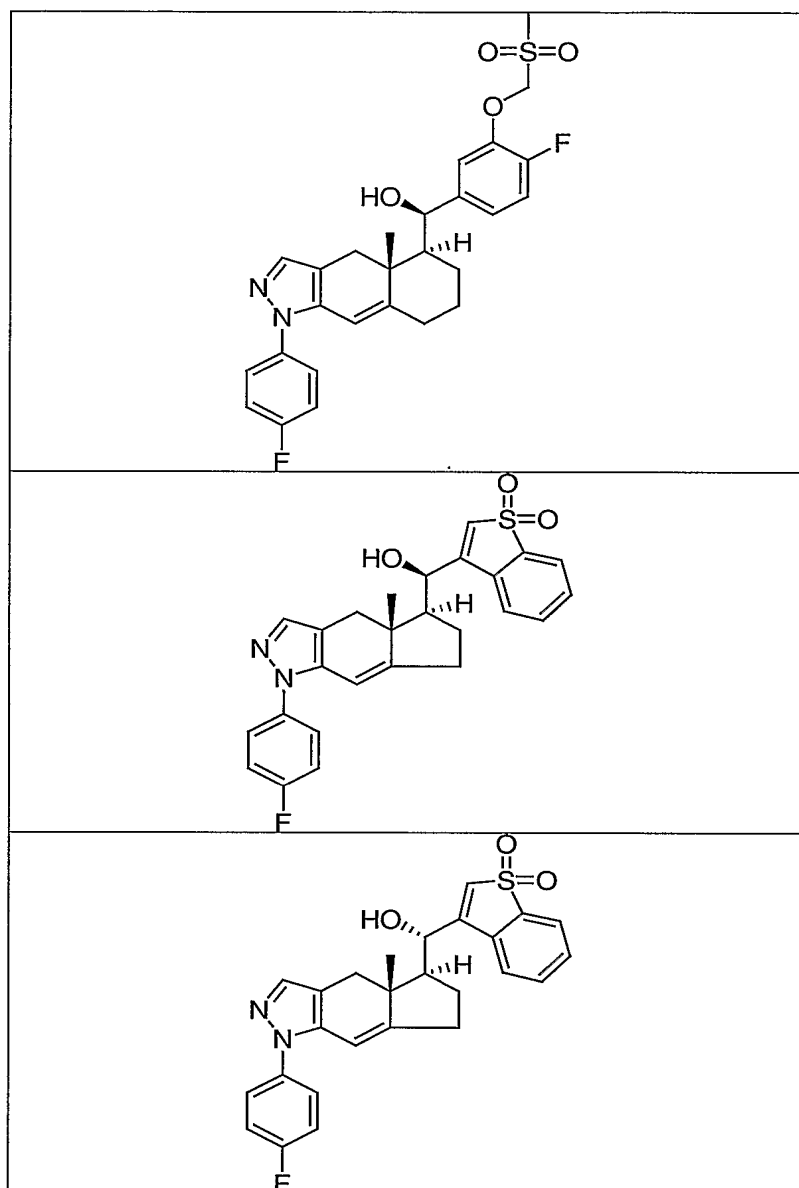






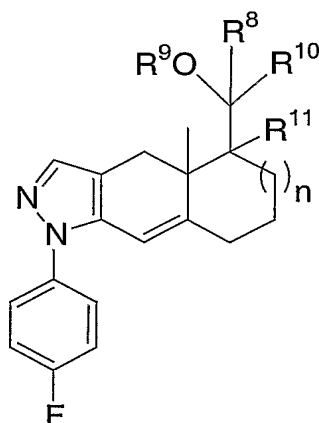






or a pharmaceutically acceptable salt of any of the above.

19. A compound according to Claim 1 of Formula III:



III

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

5 n is 0 or 1,

R⁸ is hydrogen or methyl,

R⁹ is hydrogen or methyl or

10

R⁸ and R⁹ may be joined together with the oxygen atom shown in Formula III to form a carbonyl group;

R¹⁰ is selected from the group consisting of:

15

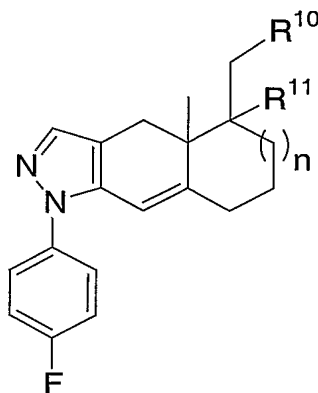
- (1) phenyl,
- (2) naphthyl,
- (3) pyridyl,
- (4) furyl or benzofuryl,
- (5) thienyl or benzothienyl, or the S,S-dioxide thereof,
- (6) benzyl,
- (7) quinoline,
- (8) thiazolyl or benzothiazolyl, and
- (9) phenylsulfonylmethyl or phenylsulfonylethyl, wherein

20

25 groups (1) to (9) are optionally substituted with 1 to 3 substituents independently selected from the group consisting of:

- 5 (a) halo,
 (b) trifluoromethyl,
 (c) trifluoromethoxy,
 (d) -N(R¹⁴), wherein each R¹⁴ is independently hydrogen or
 C₁₋₄alkyl,
 (e) pyrrolyl,
 (f) methoxy, ethoxy or isopropoxy, each optionally
 substituted with a substituent selected from: methoxy, benzyl, cyclopropylmethyl,
 10 cyano, methylthio, methylsulfinyl and methylsulfonyl,
 (g) methyl,
 (h) vinyl and
 (i) hydroxy, and
- 15 R¹¹ is hydrogen or halo.

20. A compound according to Claim 1 of Formula IV:



IV

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0 or 1,

R¹⁰ is selected from the group consisting of:

- (1) -CH(OR¹³)-aryl, wherein aryl is phenyl or naphthyl,

- (2) $-\text{CH}(\text{OR}^{13})\text{-HET}$, and
(3) $-\text{CH}(\text{OR}^{13})\text{-C}_{1-4}\text{alkyl}$ or $-\text{CH}(\text{OR}^{13})\text{-C}_{2-4}\text{alkenyl}$, said
 $-\text{CH}(\text{OR}^{13})\text{-C}_{1-4}\text{alkyl}$ or $-\text{H}(\text{OR}^{13})\text{-C}_{2-4}\text{alkenyl}$ optionally substituted with
phenylsulfonyl,

5

R^{13} is hydrogen or methyl,

HET is selected from the group consisting of:

- (1) pyridyl,
10 (2) furyl or benzofuryl,
(3) thienyl or benzothienyl, or the S,S-dioxide thereof,
(4) benzyl,
(5) quinoline,
15 (6) thiazolyl or benzothiazolyl,

15

said aryl or HET are optionally substituted with 1 to 3 substituents independently
selected from the group consisting of:

- (a) halo,
20 (b) trifluoromethyl,
(c) trifluoromethoxy,
(d) $-\text{N}(\text{R}^{14})$, wherein each R^{14} is independently hydrogen or
 $\text{C}_{1-4}\text{alkyl}$,
(e) pyrrolyl,
25 (f) methoxy, ethoxy or isopropoxy, each optionally
substituted with a substituent selected from: methoxy, benzyl, cyclopropylmethyl,
cyano, methylthio, methylsulfinyl and methylsulfonyl,
(g) methyl,
(h) vinyl and
30 (i) hydroxy, and

R^{11} is hydrogen or halo.

21. A pharmaceutical composition comprising a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier.

22. A method for treating a glucocorticoid receptor mediated
5 disease or condition in a mammalian patient in need of such treatment comprising administering the patient a compound according to Claim 1 in an amount that is effective for treating the glucocorticoid receptor mediated disease or condition.

23. The method according to Claim 22 wherein the glucocorticoid
10 receptor mediated disease or condition is selected from the group consisting of: tissue rejection, leukemias, lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury,
15 hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity, metabolic syndrome, inflammatory bowel disease, systemic lupus erythematosus, polyarthritis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile
20 rheumatoid arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus
25 vulgaris, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous
30 T-cell lymphoma, Human Immunodeficiency Virus (HIV), cell apoptosis, cancer, Kaposi's sarcoma, retinitis pigmentosa, cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, sleep disorders, and anxiety.

24. A method of selectively modulating the activation, repression, agonism and antagonism effects of the glucocorticoid receptor in a mammal comprising administering to the mammal a compound according to Claim 1 in an amount that is effective to modulate the glucocorticoid receptor.

(19) World Intellectual Property
Organization
International Bureau



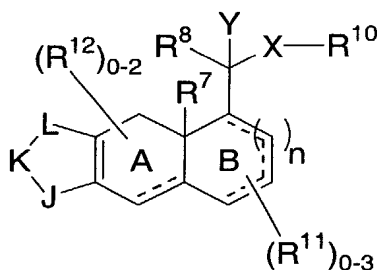
(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 2003/086294 A3

- (51) International Patent Classification⁷: **A61K 31/415** (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (21) International Application Number:
PCT/US2003/010867 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 8 April 2003 (08.04.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/371,948 11 April 2002 (11.04.2002) US
- (71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **ALI, Amjad** [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BALKOVEC, James, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **GRAHAM, Donald, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **THOMPSON, Christopher, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **QURAISHI, Nazia** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- (88) Date of publication of the international search report:
15 July 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: 1H-BENZO[F]INDAZOL-5-YL DERIVATIVES AS SELECTIVE GLUCOCORTICOID RECEPTOR MODULATORS



(57) Abstract: The present invention encompasses compounds of Formula I: (I) or pharmaceutically acceptable salts or hydrates thereof, which are useful as selective glucocorticoid receptor ligands for treating a variety of autoimmune and inflammatory diseases or conditions. Pharmaceutical compositions and methods of use are also included.



WO 2003/086294 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10867

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/415

US CL : 514/405; 548/359.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/405; 548/359.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,349,559 (BELL et al) 14 September 1982, column 6.	1-24
A	US 4,412,995 (BELL et al) 1 November 1983, columns 7-8.	1-24
A	US 4,349,558 (BELL et al) 14 September 1982, column 6.	1-24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 August 2003 (26.08.2003)

Date of mailing of the international search report

24 NOV 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Robert L. Smith

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10867

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-24
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/IS03/10867

The inventions do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding technical features that defines a contribution over the prior art. The compounds claimed contain benzindazole moiety, which does not define a contribution over the prior art (as can be seen by the compound I of CAS:113:152403). Each of the inventions in this applications represent a discrete compound which one skilled in the art which beside sharing no structural element, cannot be said to belong to a recognized class of chemical compounds. Accordingly, the unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

- I Claims 1-24, in part, drawn to products of formula I, wherein K is NR3 and J is NR1, L is C(R5)(R6), and R1, R3, R5, and R6 are not HET or alkyl-HET; X, Y, R7, R8, R10, R11, and R12 are not HET or alkyl-HET; and their methods of use.
- II Claims 1-24, in part, drawn to products of formula I, wherein L is NR5 and J is NR1, K is C(R3)(R4), and R1, R3, R4, and R5 are not HET or alkyl-HET; X, Y, R7, R8, R10, R11, and R12 are not HET or alkyl-HET; and their methods of use.
- III Claims 1-24, in part, drawn to products of formula I, wherein K is NR3 and J is NR1, L is C(R5)(R6), and R1, R3, R5, and R6 are not HET or alkyl-HET; X, Y, R7, R11, and R12 are not HET or alkyl-HET; and R8 or R10 is thiazole; and their methods of use.
- IV Claims 1-24, in part, drawn to products of formula I, wherein K is NR3 and J is NR1, L is C(R5)(R6), and R1, R3, R5, and R6 are not HET or alkyl-HET; X, Y, R7, R11, and R12 are not HET or alkyl-HET; and R8 or R10 is pyridine; and their methods of use.
- V Claims 1-24, in part, drawn to products of formula I, and not embraced in Group I-IV; and their methods of use.

Claims 1-24 are drawn to more than one inventive concept (as defined by PCT Rule 13), and accordingly, a restriction is required according to the provision of PCT Rule 13.2.

PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (requirement of unity of invention).

PCT Rule 13.2 state that unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Annex. B, Part 1(b), provides that "special technical features" mean those technical features, which, as a whole, define a contribution over the prior art.

Annex B, Part I(e), provides combinations of different categories of claims and states:

"The method for determining unity of invention under Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application:

(I) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product, or

(II) in addition to an independent claim for a given process, an independent claim for an apparatus or means specifically designed for carrying out the said process, or

(III) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for an apparatus or means specifically designed for carrying out the said process..."

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 C.F.R. 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Claims 1-24 are generic to a plurality of disclosed patentably distinct species comprising for example, the compounds designated as (1) a compound 1, 2 diazole tricyclo ring system not having other heterocycle ring, (2) compound 1, 3 diazole tricyclo ring system not having other heterocycle ring, (3) a compound 1, 2 diazole tricyclo ring system having another heterocycle ring thiazole, (4) a compound 1, 2 diazole tricyclo ring system having another heterocycle ring pyridine.

INTERNATIONAL SEARCH REPORT

1503/10867

The inventions do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding technical features that defines a contribution over the prior art. The compounds claimed contain benzindazole moiety, which does not define a contribution over the prior art (as can be seen by the compound I of CAS:113:152403). Each of the inventions in this applications represent a discrete compound which one skilled in the art which beside sharing no structural element, cannot be said to belong to a recognized class of chemical compounds. Accordingly, the unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.